University of Alberta

Synthetic Studies toward *Traversianal*, Intermolecular Trapping of Nazarov Intermediate by Organic Azides, and Attempted Generation of Dialkoxycarbene from Thionocarbonates

by

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To My Family: Yuhua, Lianqing, Jin, Weihan

ABSTRACT

The synthetic studies toward *traversianal*, a diterpenoid fungal metabolite isolated from *Cercospora traversianal,* are described. A novel strategy to diastereoselectively assemble the functionalized 5-8-5 tricyclic system by a crossed intramolecular [4+4]-photocycloaddition has been developed. The key precursors for the photoreaction are fused bicyclic pyran-2-ones with pendant furan side chains and an oxygenated stereogenic center adjacent to the pyranone ring oxygen. These substrates were prepared *via* $FeCl_3$-catalyzed Michael addition of pyrone to enone. Irradiation of these compounds furnished the corresponding lactone-bridged tricyclic [4+4]-cycloadducts with 7:1 facial selectivity due to the introduction of a bulky TBDPS silyl group on the oxygenated stereocenter adjacent to C-6 of the pyrone ring. Interestingly, X-ray crystal structures of derivatives of two major isomers indicate that the furan approaches the pyrone from the same face as the OTBDPS group. Cleavage of the bridging lactone and bridging ether in the cycloadducts was successfully achieved. One of these advanced intermediates is suitable for further elaboration to complete the total synthesis of *traversianal*.

Chapter 3 describes intermolecular trapping of the Nazarov intermediate with an alkyl azide. This example of the "interrupted" Nazarov reaction involves trapping of the oxyallyl cationic intermediate by an alkyl azide followed by rearrangement to yield lactam products. Four dienones and three different primary alkyl azides were examined to give satisfactory results. All of the examples demonstrate complete regioselectivity and some cases show complete stereoselectivity.

In Chapter 4, an alternative route to generate nucleophilic dialkoxycarbenes by using thionocarbonates and phosphites was investigated. A variety of phosphites and phosphine reagents were examined. Unfortunately, the desired [4+1]-cycloadduct was not observed.

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LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Anal.	Elemental analysis
Ar	Aryl
Bn	Benzyl
brs	Broad singlet
Bz	Benzoyl
Calcd.	Calculated
cat.	Catalyst
COD	Cyclooctadiene
COSY	Homonuclear correlation spectroscopy
conc.	Concentrated
d	Doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DIBAL	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	4-(*N,N*)-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
EI	Electron Impact
eqiv	Equivalent(s)
ESI	Electronspray ionization
FTIR	Fourier-Transform Infrared
h	Hour(s)
HMQC	Heteronuclear multiple quantum coherence
HRMS	High resolution mass spectrometry

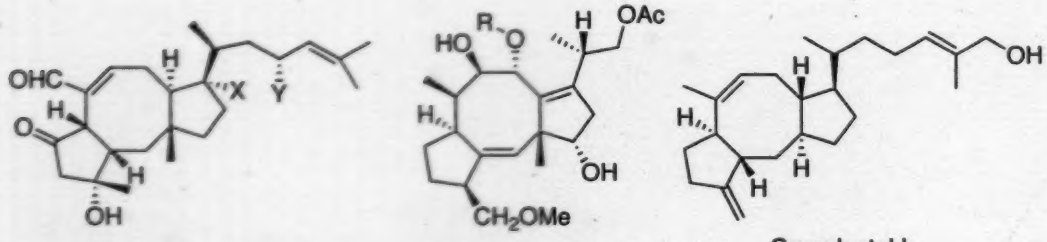
Hz	Hertz
IR	Infrared
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
mCPBA	3-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmol	Millimole(s)
MeOH	Methanol
MOM	Methoxymethyl
m.p.	Melting point
MS	Mass spectrometry
Ms	Methane sulfonyl
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect
OTf	Trifluoromethanesulfonate
PCC	Pyridinium chlorochromate
Ph	Phenyl
ppm	Parts per million
q	Quartet
R	Generic alkyl group
R_f	Retention factor
rt	Room temperature
s	Singlet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethyl

TBDPS	*tert*-Butyldiphenylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
TsOH	*p*-Toluenesulfonic acid

CHAPTER 1

RECENT APPROACHES TO 5-8-5 RING SYSTEMS

The formation of 5-8-5 ring systems has received considerable attention in the synthetic community. A number of complex and biologically active natural products, such as the ophiobolins,[1] fusicoccin and the ceroplastol family,[2] contain this type of skeleton (Scheme 1). The major synthetic challenge presented by these natural products is the construction of the cyclooctane ring. The synthesis of medium-sized rings is hindered by substantial entropic barriers and enthalpic constraints.[3] For example, both transannular interaction and Pitzer strain are greatest when forming eight-membered rings. Therefore, direct ring formation from an acyclic precursor often suffers from poor conversion. Stimulated by these challenging natural products with promising biological activities, many research groups have developed new approaches toward the synthesis of this cyclooctane ring system.[4] This review will focus on the work which is particularly relevant to the construction of 5-8-5-ring systems.



Ophiobolin A X = Y = O
Ophiobolin B X = OH, Y = H
Ophiobolin C X = Y = H

Fusicoccin A
R = sugar residue

Ceroplastol I

Scheme 1

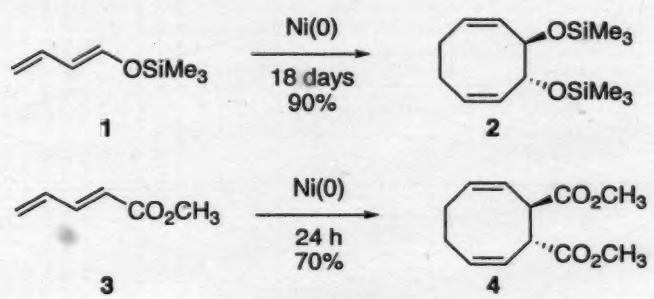
1.1 [4+4] Cycloadditions

Cycloadditions, especially higher order cycloadditions, constitute one of the most powerful methods for the synthesis of cyclooctanoids. In analogy to the Diels-

Alder reaction, two smaller fragments with extended π-bond arrays assemble to make two new carbon-carbon bonds in a single step. The cycloaddition reaction could overcome enthalpic barriers inherent in the ring closing strategy. Transannular interactions are also diminished in the cycloaddition approach due to the sterically less demanding sp^2 carbons on the conjugated systems compared to an sp^3 carbon backbone. However, entropic factors involved in the arrangement of two π-systems within bond-forming distance are more complex in the higher order cycloaddition reaction. Increased entropic demands often result in poorer periselectivity. There are two basic strategies to solve the entropic problem. One approach involves metal templates, which have been used in the [4+4]-, [6+2]-, and [6+4]-cycloaddition reactions. Another approach incorporates the conjugate π-systems into existing rings. Both approaches have seen great success in higher order cycloadditions.

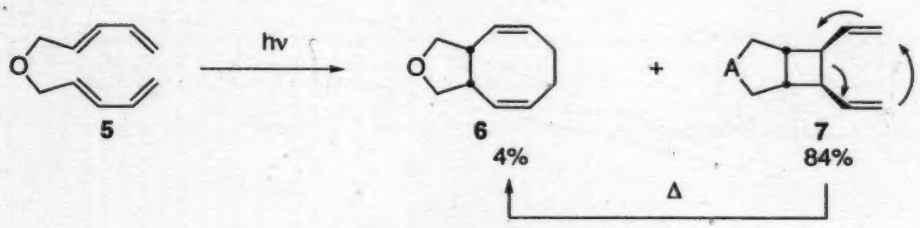
1.1.1 Transition Metal Mediated [4+4]-Cycloadditions

Tenaglia and co-workers found functionalized dienes could be dimerized in the presence of Ni(0) catalyst to afford regio- and stereo- controlled cyclooctadiene derivatives.[5,6] Ni(0) can be obtained either by reduction of $Ni(acac)_2$ by Et_2AlOEt in the presence of PPh_3 or with preformed $Ni(COD)_2$. When methoxycarbonyl or a trimethylsiloxy group was bonded to the terminal carbon of the diene, such as substrates **1** and **3**, the products **2** and **4** can be obtained with complete regio- and stereo-selectivity , and in good yields (Scheme 2).



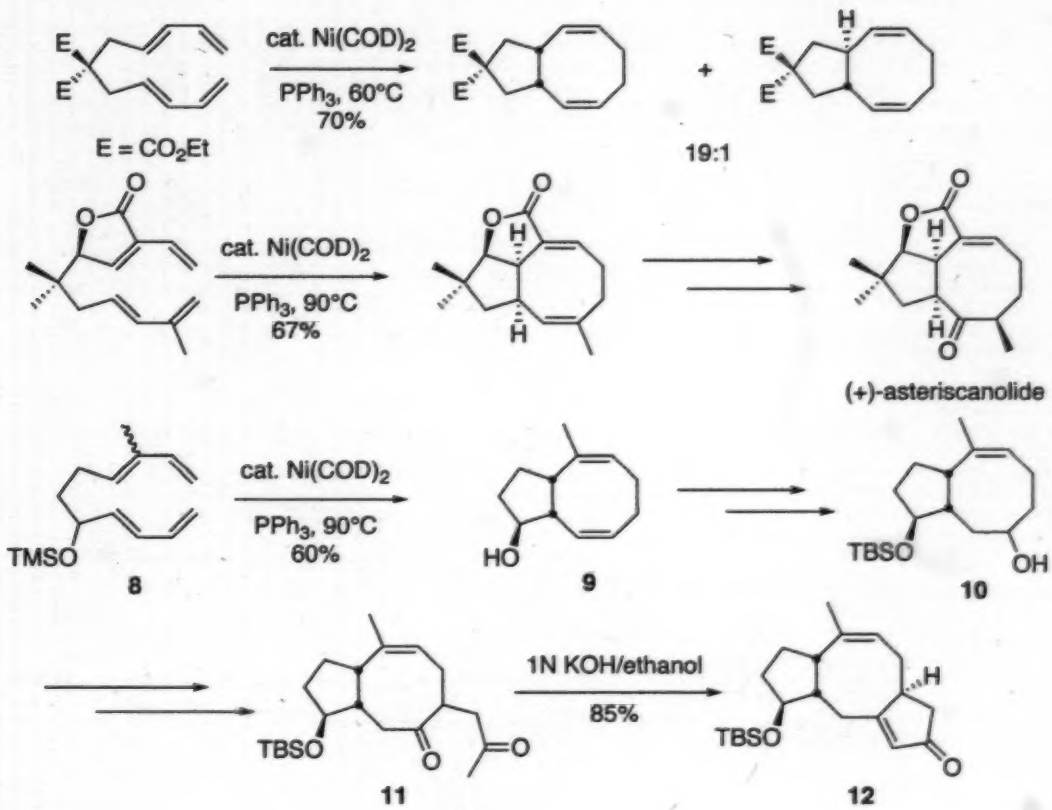
Scheme 2

Wender and co-workers have investigated the intramolecular photocycloaddition of two 1,3 diene moieties **5** tied together with an ether tether; however, the desired [4+4] cycloadduct **6** was obtained in low yield. The major product of this reaction was a divinyl cyclobutane **7** resulting from [2+2] cycloaddition. Due to the ring strain of cyclobutane, the [2+2] cycloadduct **7** could be converted into the cyclooctadiene **6** through a [3,3]-sigmatropic rearrangement (Scheme 3).[7]



Scheme 3

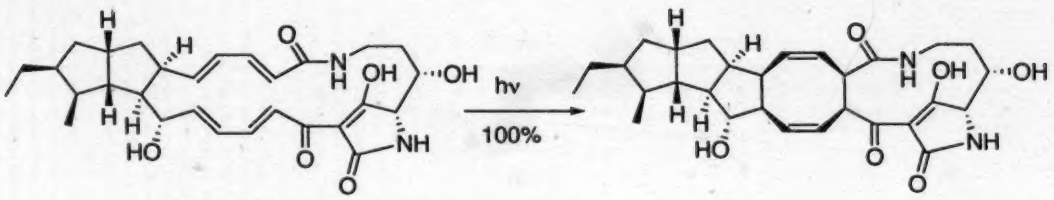
Wender and co-workers attributed the low yield of the [4+4]-addition product to the entropic demand presented by bringing the termini of both diene moieties within bonding distance. By employing $Ni(COD)_2$ as a transition metal catalyst, Wender and co-workers has successfully overcome the barriers that impeded [4+4] cycloaddition of acyclic 1,3-dienes. The metal template provided direct access to the [4+4] cycloaddition product in high yield and excellent diastereoselectivity.[8,9] This methodology has been applied to the total synthesis of (+)-asteriscanolide.[10,11] Aimed at the synthesis of diterpenes such as fusicoccins and sesterterpenes such as ophiobolines, Ni-catalyzed dimerization was also applied to the synthesis of the 5-8-5-structural core of the fusicoccins and ophiobolines.[12] The 5-8-bicyclic compound **9** was constructed through a Ni-catalyzed [4+4]-cycloaddition of **8**. After several steps, compound **9** was converted to compound **10** for further modification. The third ring in the carbon framework was introduced after the [4+4]-cycloaddition by an aldol condensation (Scheme 4). Treatment of diketone **11** with KOH resulted in cyclopentane annulation product **12** in good yield.



Scheme 4

1.1.2 [4+4]-Photocycloaddition

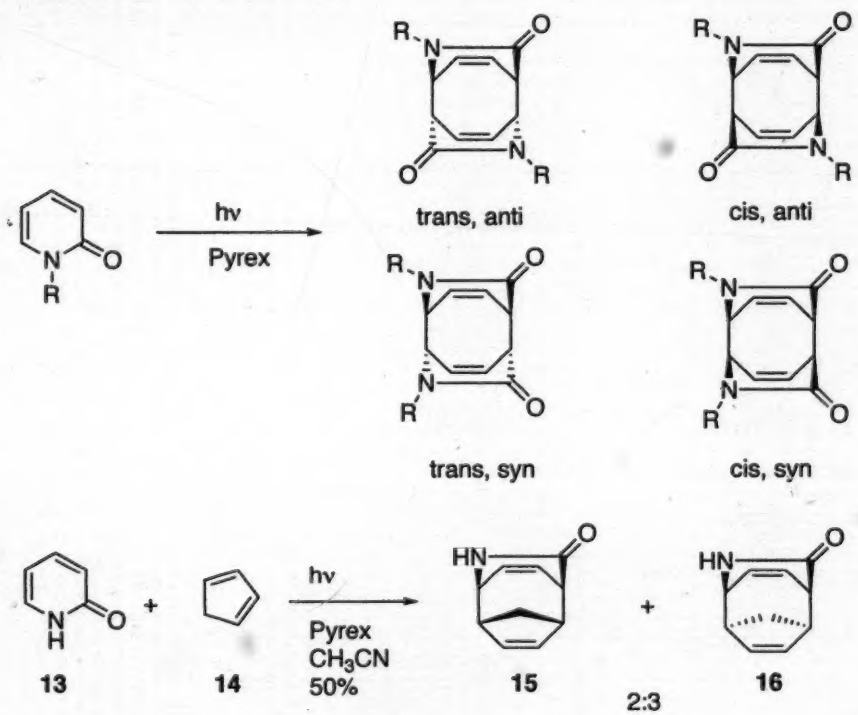
[4+4]-Photocycloaddition has been investigated in a number of substrates, such as aromatic compounds,[13] orthoquinodimethanes[14,15] and 1,3 dienes.[16-18] Most of these reactions are inefficient and have limited synthetic potential. However there is one interesting example found in the natural product alteramide A, which has been shown to convert into a hexacyclic derivative in MeOH when exposed to daylight at room temperature for two days (Scheme 5).[19] The efficiency of this process is likely due to the conformation of the macrolactam that brings the two diene moieties together.



Alteramide A

Scheme 5

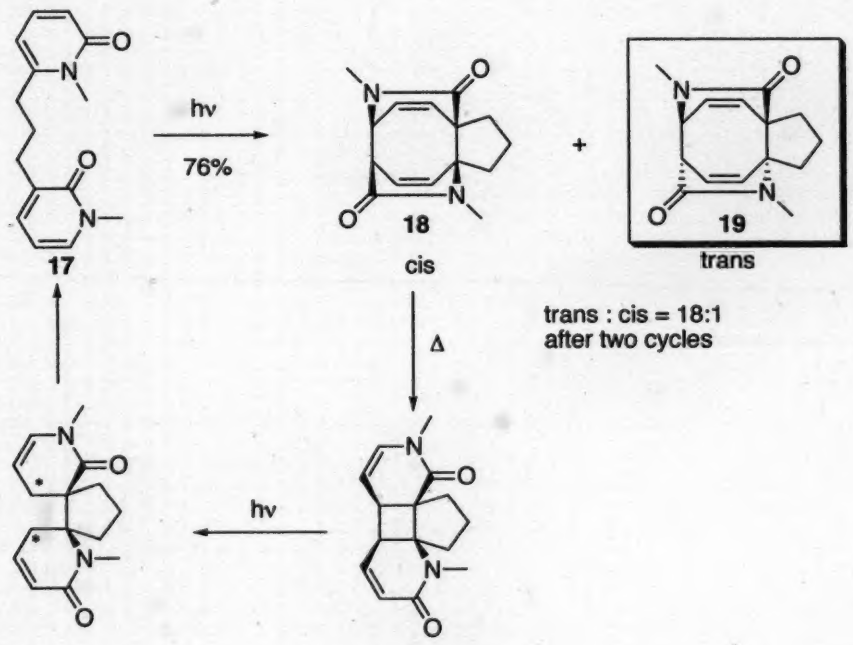
Photodimerization of 2-pyridones usually generates four isomeric cycloadducts, the *trans*- and *cis*- diastereomers of both head-to-head and head-to-tail regioisomers. Major stereoisomeric isomers were *trans-anti* and *cis-anti* dimers. By changing the solvent, concentration, and substitution of 2-pyridone, minor *trans-syn* and *cis-syn* products were decreased or avoided entirely.[20] Crossed [4+4] cycloaddition between 2-pyridone **13** and cyclopentadiene **14** has been observed as well.[21] Irradiation resulted in the two isomers **15** and **16** in a ratio of 2:3 and a combined yield of 50% (Scheme 6).



13 **14** **15** **16**

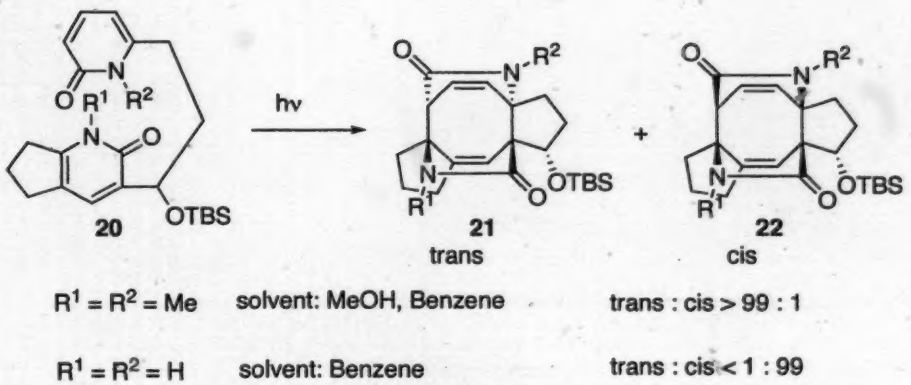
Scheme 6

Sieburth and co-workers have investigated the intramolecular version of 2-pyridone [4+4]-dimerization.[22-25] A mixture of *trans*- and *cis*- isomers **18** and **19** was obtained in the photocycloaddition of 2-pyridones **17** tethered by a three-carbon chain. Enrichment of the *trans* isomer **19** was achieved *via* a photo-thermal equilibrium process. The *cis* isomer **18** could undergo a Cope rearrangement at 60°C followed by a photocleavage to reform the 2-pyridones **17**. The starting material **17** could then participate in a new [4+4] photocycloaddition. After two cycles of successive irradiation and heat, the ratio was increased from 2:1 (*trans* : *cis*) to 18:1 (Scheme 7).[26]



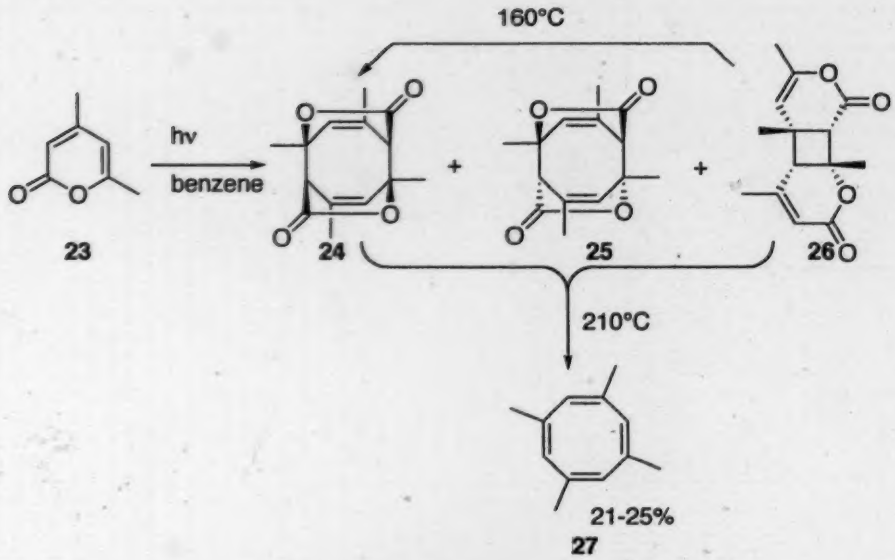
Scheme 7

Sieburth and co-wofkers then applied intramolecular [4+4] dimerization towards the synthesis of fusicoccin A (Scheme 8).[27] The 5-8-5-ring skeleton was achieved by irradiation of two tethered 2-pyridones **20**. The bulky TBS group on the tether directed the approach of the 2-pyridones to give only two of the four possible diastereoisomers **21** and **22**. The ratio of *trans/cis* products (**21/22**) depends on the solvent and substituents on the 2-pyridone units.



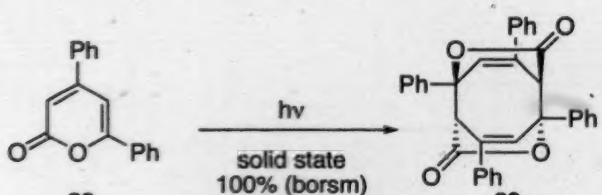
Scheme 8

Over 40 years ago, de Mayo and co-workers first reported that cyclooctanoids could be synthesized from a [4+4]-photocycloaddition of two 2-pyrone molecules. Irradiation of concentrated solutions of 4,6-dimethylpyran-2-one **23** in benzene resulted in two diastereomeric [4+4]-adducts **24** and **25,** and an isomeric [2+2]-adduct **26** (Scheme 9).[28] Upon heating the product mixture at 160°C, the [2+2]-adduct **26** was converted to the *endo* adduct **24** *via* a [3,3]-sigmatropic rearrangement. Continued heating at 210°C afforded useful amounts of tetramethyl cyclooctatetraene **27**. However, when the same strategy was applied to other 2-pyrone substrates, the reaction was not as successful.



Scheme 9

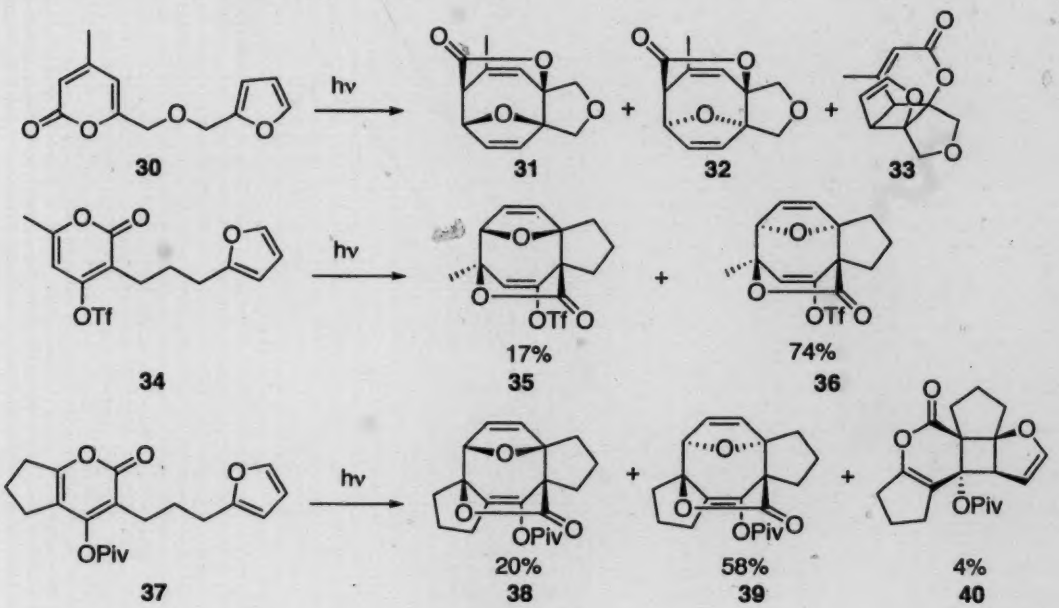
Rieke and co-workers have reported another example of 2-pyrone photodimerization (Scheme 10).[29] Irradiation of 4,6-diphenylpyran-2-one **28** in the solid state resulted in a single *exo* [4+4]-diastereomer **29**. However, under the same conditions, irradiation of 4,6-dimethylpyran-2-one **23** only resulted in a 2% yield of the [4+4]-cycloadduct.



Scheme 10

West and co-workers have demonstrated the utility of a crossed [4+4]-intramolecular photocycloaddition of 2-pyrones tethered with a furan moiety at the 6-position (Scheme 11).[30-32] Irradiation of the furan-tethered pyrone **30** furnished three adducts **31**, **32** and **33**, as a result of *exo* [4+4]-, *endo* [4+4]-, and [2+2]-cycloadditions.[30] The ratio of products obtained from this reaction is solvent dependent and higher yields of [4+4] edno-adduct **31** could be obtained upon

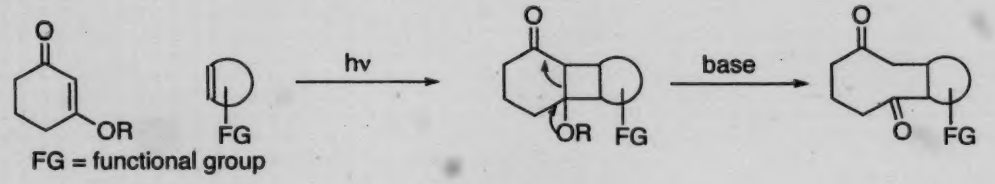
irradiation in aqueous LiCl. Intramolecular photocycloaddition reactions of 2-pyrones **34** and **37** tethered at the 3-position were also examined. Irradiation of **34** gave a mixture of two isomers **35/36** at a ratio of 1:4.[31] Photocycloaddition of **37** afforded two [4+4]-photocycloadducts **38/39** and one [2+2]-cycloadduct **40**.[33] Among these samples are cycloadducts containing a 5-8-5 ring system, which implies considerable synthetic potential toward the synthesis of fusicoccins and ophiobolins.



Scheme 11

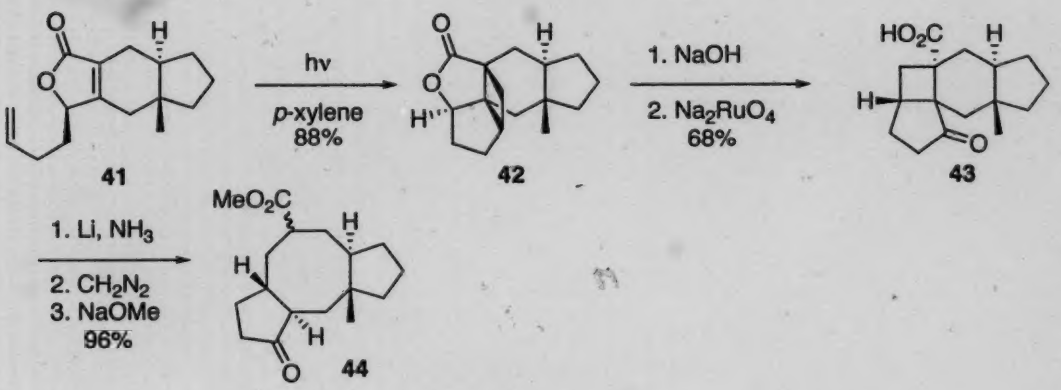
1.2 [2+2] Photocycloaddition/Fragmentation

[2+2]-Photocycloaddition of an enone and olefin followed by cyclobutane ring opening is known as the de Mayo reaction (Scheme 12).[34,35] It has been effectively employed for the construction of cyclooctanoid rings.



Scheme 12

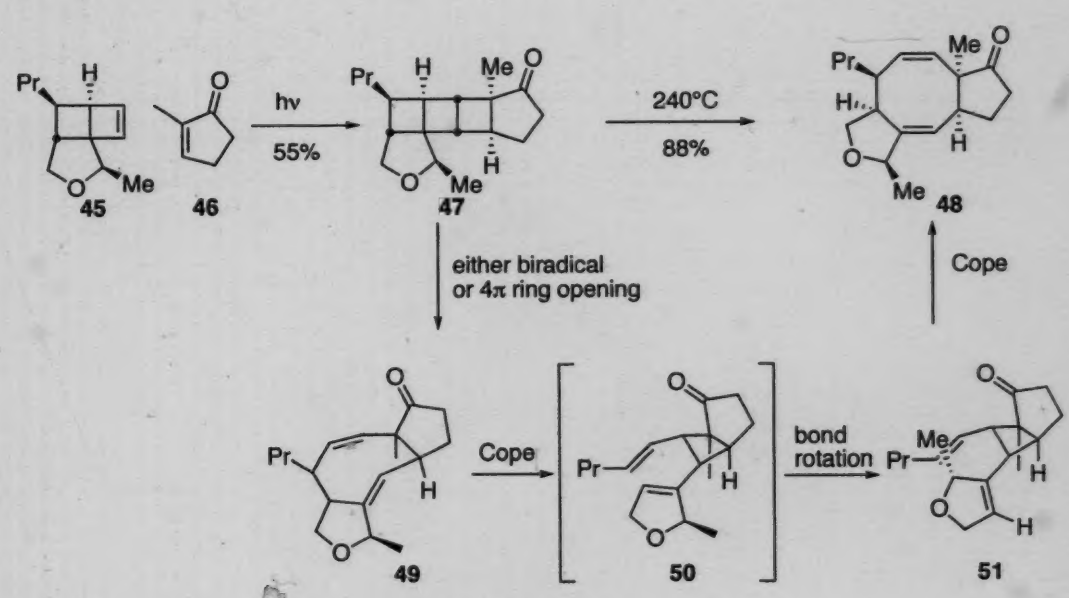
Coates and co-workers have applied a variation of this methodology to the synthesis of the tricyclic 5-8-5 nucleus of ophiobolins (Scheme 13).[36] Irradiation of an alkenyl butenolide **41** in *p*-xylene resulted in the intramolecular [2+2]-cycloadduct **42** in good yield. Subsequent hydrolysis and oxidation of the resulting lactone **42** afforded the keto acid which has then treated with lithium in liquid ammonia to generate the 5-8-5 ketone in excellent yield. The carboxylic acid was then converted to an ester by treatment with diazomethane. Epimerization under basic conditions gave the desired *trans*-fused compound **44**.



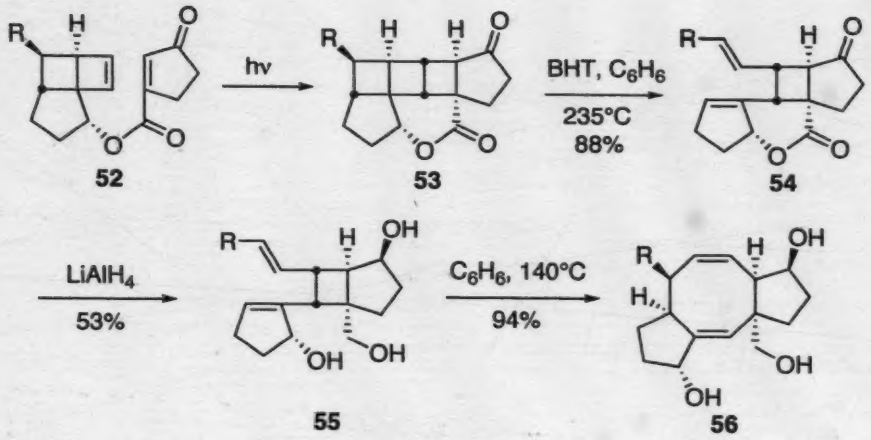
Scheme 13

Snapper and co-workers have reported a new strategy for preparing functionalized 5-8-5-ring systems by a photocycloaddition/fragmentation sequence (Scheme 14).[37] Irradiation of tricyclic cyclobutene **45** and cyclopentenone **46** resulted in the [2+2]-photocycloaddition product **47** as a single isomer. Upon heating, the resulting strained cycloadduct **47** fragmented to give the desired tricyclic product **48** in good yield. The key intermediate **50** in this fragmentation is proposed

to be a 1,5-diene, shown in the brackets. Opening of the central cyclobutane could proceed by a stepwise, biradical process or a symmetry-allowed [$\sigma 2_a + \sigma 2_s$] ring opening to give the tricyclic intermediate **49** that rearranges to afford the key 1,5-diene **50**. Rotation of the resulting 1,5-diene from a boat to a chair conformation allowed the second Cope rearrangement which provided the 5-8-5-ring system. The proposed 1,5-diene intermediate was isolated in the intramolecular version (Scheme 15).[38,39] Formation of cyclooctadiene product through a Cope rearrangement of 1,5-diene **54** is inhibited by the geometric constraints of the lactone. After cleavage of the lactone by $LiAlH_4$, Cope rearrangement of **55** did occur to afford the 5-8-5-ring structure **56**.



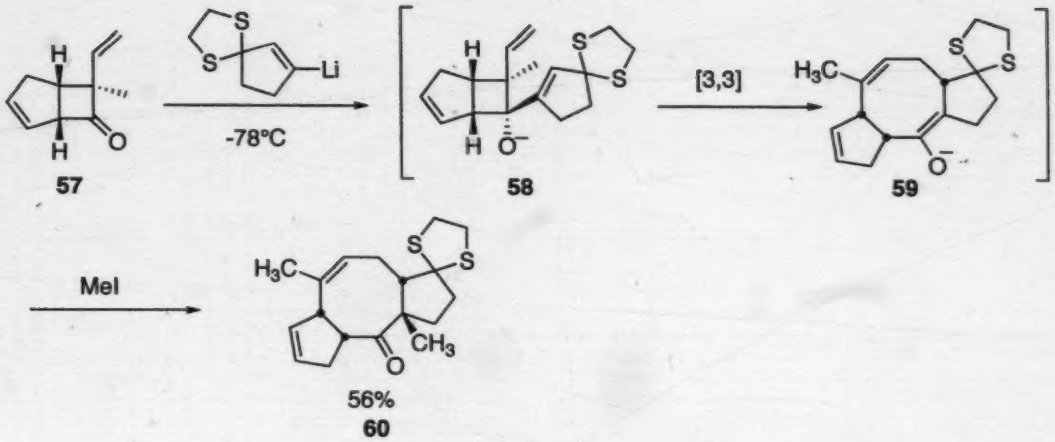
Scheme 14



Scheme 15

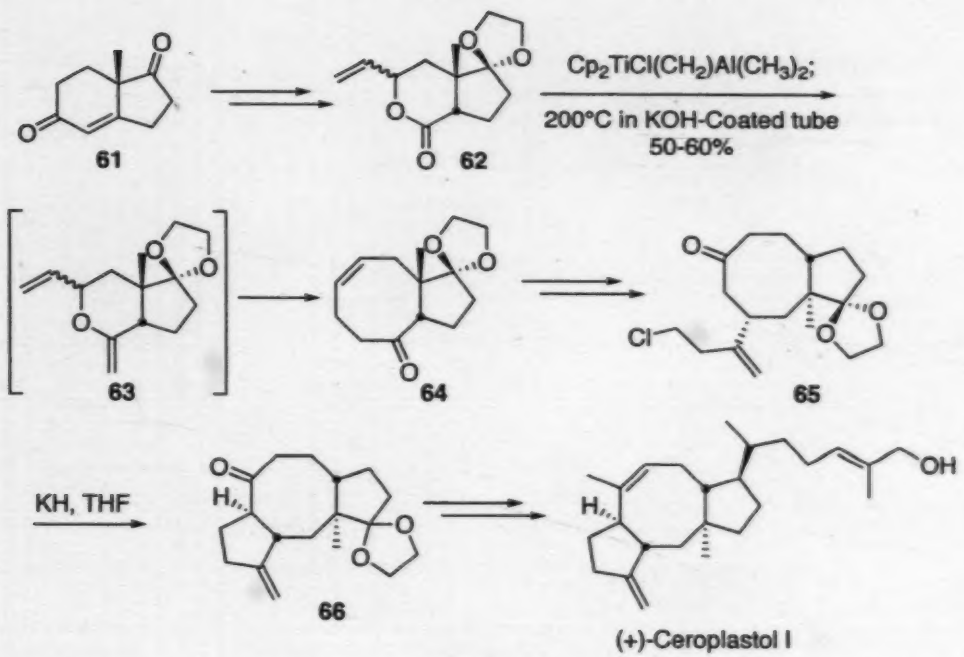
1.3 [3,3]-Sigmatropic Rearrangement

Oxy-Cope rearrangement offers a powerful strategy for the construction of polycyclic frameworks. The benefits of an oxy-Cope strategy include a high level of chirality transfer, regiocontrol, and generation of the carbonyl group in a new structural context. Paquette and co-workers have exploited the anionic oxy-Cope strategy to construct a 5-8-5 fused ring system in a stereoselective fashion (Scheme 16).[40,41] Nucleophilic addition of cyclopentenyllithium to the bicyclic ketone **57** from the *exo* face resulted in a 1,5-diene intermediate **58**, which underwent a [3,3]-sigmatropic process to afford an enolate intermediate **59**. At this point, methyl iodide was introduced, and a single product **60** was isolated in 56% yield.



Scheme 16

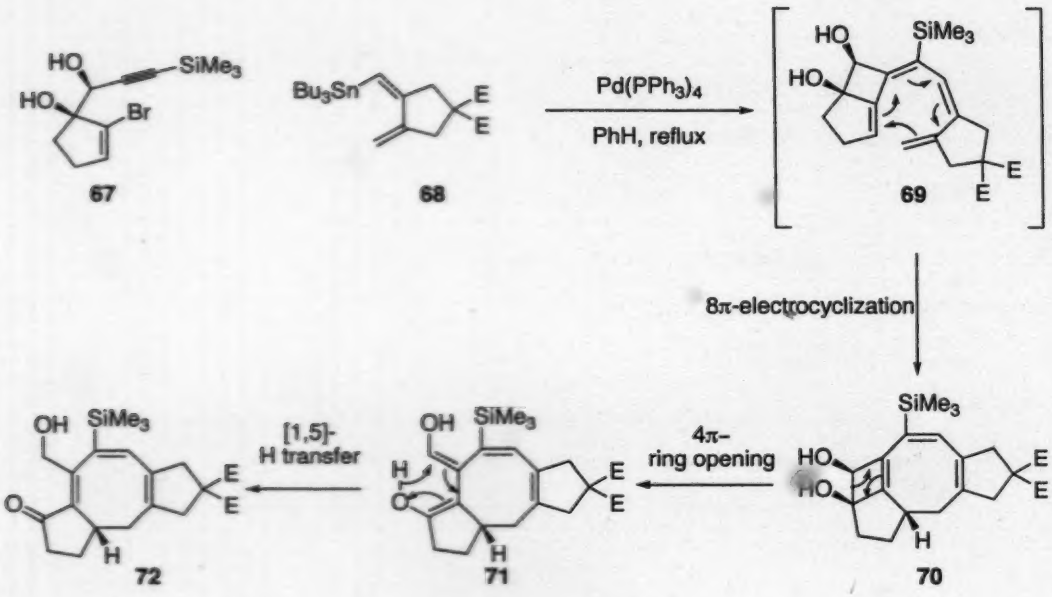
Recently, Paquette and co-workers have accomplished the synthesis of (+)-Ceroplastol I.[42] The eight-membered ring was constructed through a two carbon intercalation employing a [3,3]-rearrangement process. The five-membered ring was constructed through an intramolecular alkylation process. The key precusor was synthesized from optically pure diketone **61**. Tebbe olefination followed by Claisen rearrangement gave fused cyclooctenone **64** in 50-60% yield. Then cyclooctenone **65** was elaborated to tricyclic compound **66** via cyclopentane annulation. Subsequent functional group manipulation of tricyclic compound furnished (+)-Ceroplastol I (Scheme 17).



Scheme 17

1.4 8π-Electrocyclization

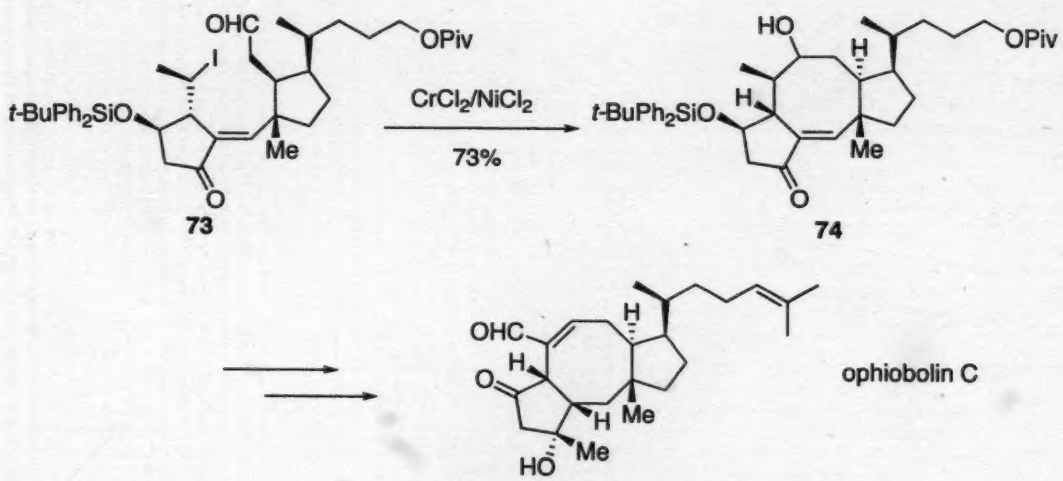
Access to the tricyclic core of the ophiobolins was achieved by 8π-electrocyclization. Suffert and co-workers have used a 4-exo-dig cyclocarbopalladation/8π electrocyclization sequence to rapidly assemble 5-8-5 ring systems (Scheme 18).[43] The 4-exo-dig cyclocarbopalladation of vinyl bromide **67** followed by a coupling reaction with vinyl stannane **68** in the presence of $Pd(PPh_3)_4$ resulted in a bicyclic product **69**, which underwent rapid 8π-electrocyclization to give a strained tetracyclic derivative **70**. The resulting cyclooctatriene **70** proceeded to undergo 4π-electrocyclic ring opening to give the bis(enol) intermediate **71** which underwent 1,5- hydride transfer to give the stable tricyclic product **72**.



Scheme 18

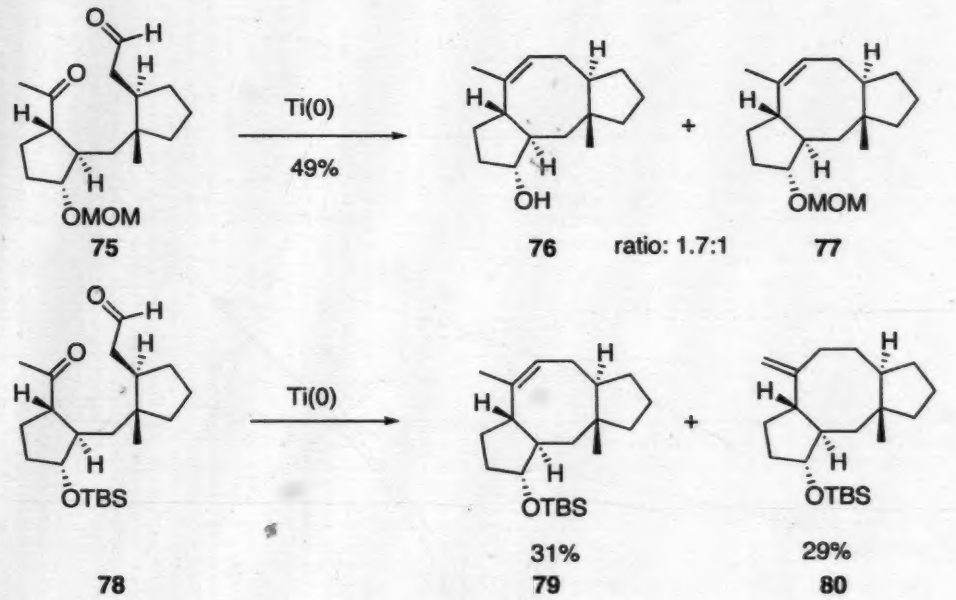
1.5 Coupling Reactions

A variety of coupling reactions, such as the Kishi reaction and McMurry coupling, have been applied in the cyclooctanoid synthesis. Kishi and co-workers have developed a methodology for making eight-membered rings based on the coupling of alkyl halides with a carbonyl group.[44] This methodology was successfully employed in the total synthesis of ophiobolin C (Scheme 19).[45] The key bond formation was achieved using an intramolecular $NiCl_2/CrCl_2$ mediated coupling reaction. The cyclized product **74** was obtained in 73% yield as a single diastereomer. After the elaboration of functional groups, the resulting tricyclic compound was converted into ophiobolin C.



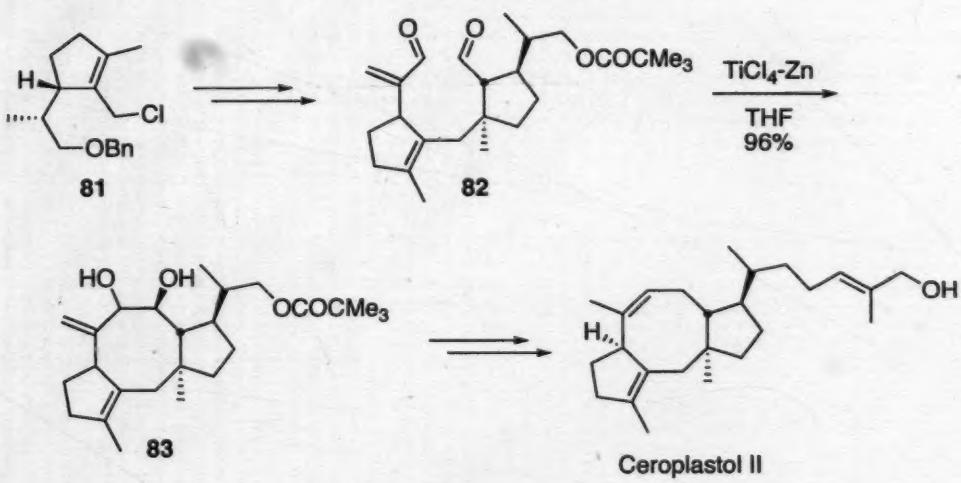
Scheme 19

Another well-known coupling reaction is the McMurry coupling. McMurry has observed that the coupling of two electrophilic centers (i.e, carbonyls) in the presence of low valent titanium metal is quite useful in the construction of eight-membered rings.[46,47] Titanium-mediated coupling reactions result in olefinic or diol products depending on the reaction conditions.[48-50] Dauben and co-workers have applied the McMurry coupling to the synthesis of ceroplastin, an ophilbolane sesterterpene (Scheme 20).[51] Treatment of an appropriately substituted dicyclopentane **75** with titanium metal resulted in a 5-8-5 fused ring skeleton in 49% yield. The free alcohol product **76** was favored over retention of the MOM ether **77** by a ratio of 1.7:1. Snider and Yang used a similar strategy with TBDMS as the protecting group.[52] Treatment of the dicarbonyl compound **78** with low-valent titanium prepared from $TiCl_3$-DME and zinc-copper couple resulted in the desired cyclooctene **79** in 31% yield and unexpected methylenecyclooctane product **80** in 29% yield. Observation of the side-product **80** may be attributed to an acid-catalyzed isomerization of the alkene during the McMurry cyclization.



Scheme 20

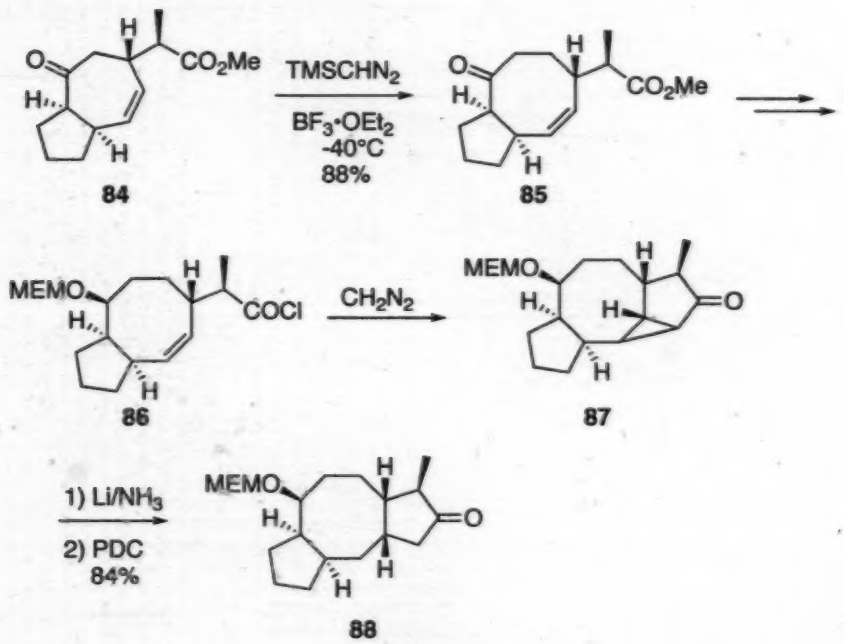
Kato and Takeshita have successfully employed McMurry coupling to the synthesis of ceroplastol II.[53] The key precursor dialdehyde **82** underwent a titanium mediated reductive cyclization under dilute conditions to give a single glycol **83** in excellent yield. After the elaboration of functional groups, the resulting glycol was converted into ceroplastol II for the first time (Scheme 21).



Scheme 21

1.6 Ring Expansion

Rigby reported a strategy to construct the 5-8-5-ring system by ring expansion.[54] Treatment of the 5-7 bicyclic compound **84** with trimethylsilyl diazomethane in the presence of $BF_3{\cdot}OEt_2$ at -40°C resulted in a one carbon ring expansion to the cyclooctanone **85** in 88% yield (Scheme 22). Treatment of acid chloride **86** with diazomethane resulted in a cyclopropanation product **87**. Reductive cleavage of the cyclopropane bond under dissolving metal conditions followed by PDC oxidation, afforded tricyclic ketone **88** in 84% yield.

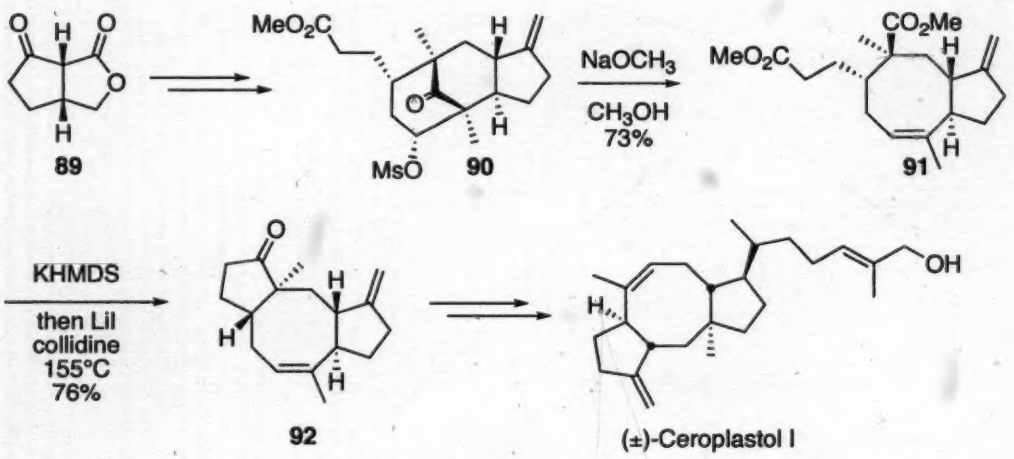


Scheme 22

1.7 Fragmentation

Boeckman and co-workers reported the first total synthesis of (±)-ceroplastol I.[55] The eight-membered ring was constructed *via* fragmentation of a functionalized bicyclo[3.3.1] nonanone system. The annulation of the five-membered ring was accomplished by Dieckman condensation. The key precursor **90** was prepared from known racemic β-ketolactone **89**. Treatment of **90** with excess $NaOCH_3$ in CH_3OH at

reflux resulted in the desired cleavage to afford **91** in 73% yield. The resulting bicyclic compound **91** underwent a Dieckman condensation and immediate decarboxylation to provide the tricyclic ketone **92** in 76% yield. Subsequent functional group manipulations of **92** led to natural product ceroplastol I (Scheme 23).



Scheme 23

1.8 Conclusion

Since ophiobolins and fusicoccins were discovered in the mid-1960s, a variety of approaches to the 5-8-5 ring system have been developed to synthesize these complex and bioactive natural products. To date, only ophiobolin C (Kishi), ceroplastol II (Kato and Takeshita), and ceroplastol I (Boeckman and Paquette) have been successfully synthesized. Most of the previously outlined methodologies are still in the early stages of development. They need to be utilized in natural product synthesis in order to further appreciate the scope of these methodologies. Due to the convenience and efficiency presented by these approaches, more natural targets will undoubtedly be synthesized using similar strategies.

1.9 References and Notes

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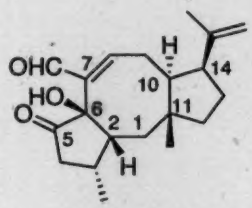
CHAPTER 2

SYNTHETIC STUDIES TOWARD TRAVERSIANAL

2.1 Background

Prompted by the successful construction of a 5-8-5-ring system through a crossed [4+4]-intramolecular photocycloaddition of 2-pyrones tethered with a furan moiety, we embarked on the synthesis of traversianal,[1] a tricyclic diterpenoid fungal metabolite of the fenugreek pathogen *Cercospora traversiana*. Traversianal has exhibited great toxicity in brine shrimp and snails, and can lyse human red blood cells at concentrations as low as 5 x 10^{-7} M. Therefore, it has the potential to be a mycotoxin.[2] This compound can also induce betacyanin leakage from beetroot slices.

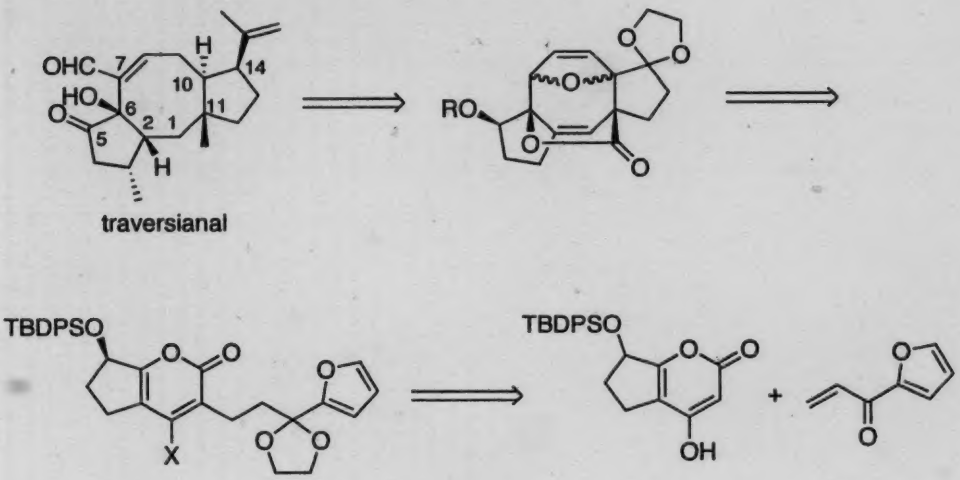


traversianal

Traversianal contains a 5-8-5-ring skeleton and six stereocenters. Our synthetic plan was based on the intramolecular [4+4]-cycloaddition of a fused bicyclic pyran-2-one tethered with furan (Scheme 1). The bulky OTBDPS group on C-5 would be used to control the facial selectivity of furan approach in the cycloaddition reaction. The resulting bridging lactone would serve as a precursor to the angular hydroxyl at C-6 and the methyl at C-11. Hydrogenation of the C-1/C-2 double bond would deliver the hydrogen from the top face to provide the desired stereochemistry and the protected ketone at C-14 would be used to open the furan bridge and introduce the isopropenyl group. Since C-7 would become an sp^2 center and C-10 would be subject to epimerization during or after reductive cleavage of the bridging ether, both *endo* and *exo* cycloadducts could be carried through the

synthesis. The key precursor for the photoreaction would be prepared by the coupling of quite simple 2-pyrone and furan fragments.

2.1.1 Retrosynthetic Analysis of Traversianal

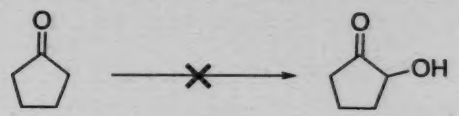


Scheme 1

2.2 Results and Discussion

To build the required fused bicyclic pyran-2-one fragment, we would need 2-hydroxycyclopentanone. Optically pure material is available by various methods,[3-5] but we chose to explore the basic strategy using the racemic series. To that end, we started with commercially available cyclopentanone **1**. Initially, making the α-hydroxyketone **2** was problematic (Table 1). Direct hydroxylation of cyclopentanone **1** was first examined. Treatment of cyclopentanone **1** with base resulted in a metal enolate that did not react with traditional hydroxylating reagents to provide the expected products. Three different bases were tested to give lithium, sodium and potassium enolates, and both Davis' oxaziridine[6] and Vedejs reagent[7] were used for the attempted hydroxylation. Unfortunately, all of the reactions were messy, so the direct α-hydroxylation strategy was not pursued.

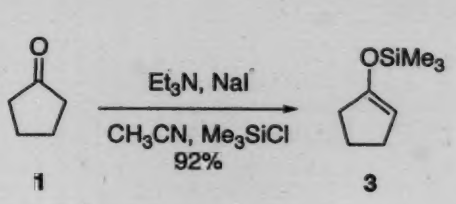
Table 1. Direct Hydroxylation of Cyclopentanone



1 2

entry	conditions	comments
1	LDA, $PhSO_2NOCHPh$, -78°C	complex mixture
2	KHMDS, $PhSO_2NOCHPh$, -78°C	complex mixture
3	NaH, $PhSO_2NOCHPh$, 0°C	complex mixture
4	KHMDS, MoOPh, -78°C	complex mixture

An indirect method to make α-hydroxyketone **2** was then investigated. Treatment of cyclopentanone **1** with chlorotrimethylsilane in the presence of triethylamine and sodium iodide resulted in silyl enol ether **3** in good yield (Scheme 2). Subsequent Rubottom oxidation of silyl enol ether **3**, using *m*-CPBA, gave a very poor yield of hydroxyketone **2**. These results might be attributed to the instability of hydroxyketone **2**, which can eliminate to generate volatile cyclopentenone or undergo a self-condensation to give hemiketal product under the reaction conditions. Attention was then turned to dihydroxylation of the silyl enol ether,[8] which is an analogous process to the Rubottom oxidation. The dihydroxylation conditions are milder than those used in the Rubottom oxidation, and under these conditions the desired hydroxyketone, **2**, was obtained in 60% yield (Table 2).



1 3

Scheme 2

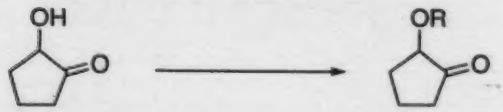
Table 2. Preparation of Hydroxy Ketone by Oxidation of Silyl Enol Ether

3 **2**

entry	conditions	comments
1	*m*-CPBA, Hexanes	10% yield
2	*m*-CPBA, CH_2Cl_2	12% yield
3	OsO_4, NMO	60% yield

Hydroxyketone **2** was then protected with a TBDPS group (entry 1, Table 3). Based on the preparation of pyrones demonstrated by Effenberger,[9] silicon protected hydroxyketone **4a** was then converted into the silyl enol ether by treatment with LDA and chlorotrimethylsilane. This methodology has previously worked well in simple case to prepare 3-hydroxy-2-pyrones. Unfortunately, treatment of this silyl enol ether with malonyl dichloride under the previously reported conditions did not result in the desired pyrone product. The two isolable products were identified as diastereomers, **5a** and **5a'**. Two molecules of malonyl dichloride condensed in the presence of the silyl enol ether to give an acid chloride intermediate shown in the brackets. The cyclopentanone was then able to react with the resulting acid chloride intermediate to afford **5a** and **5a'** (Scheme 3). One the assumption that the steric bulk of the TBDPS group might be responsible for the poor reactivity, we investigated smaller protecting groups, like TBS and MOM, **4b** and **4c** (Table 3). Unfortunately, these substrates also provided mixtures of two diastereomers analogous to **5a** instead of the expected pyrone product (Table 4). We believe that an inductive deactivation by the oxygen substituent adjacent to the carbonyl is the principal reason for the negative outcome of this annulation.

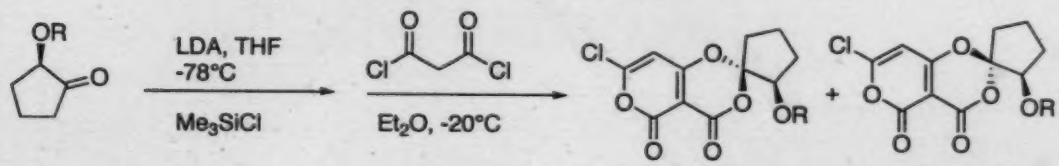
Table 3. Protection of Hydroxy Ketone



2 **4a-c**

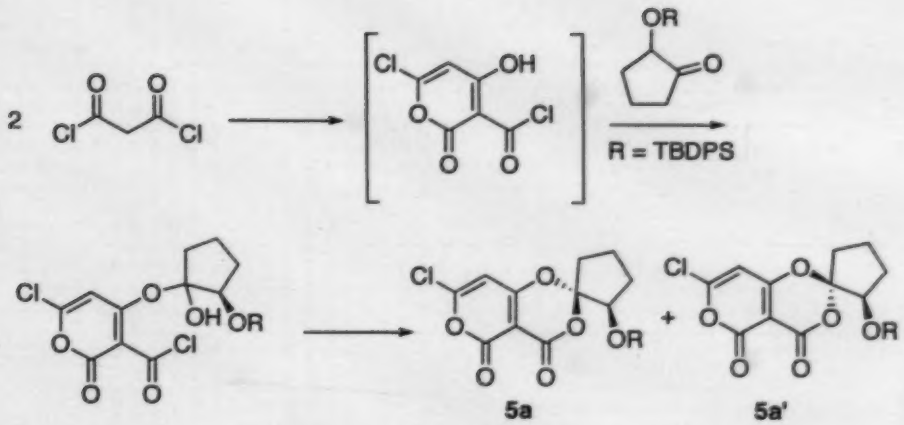
entry	R	conditions	product	comments
1	TBDPS	TBDPSCl, imidazole, DMF	**4a**	96% yield
2	TBS	TBDSCl, imidazole, DMF	**4b**	90% yield
3	MOM	MOMCl, DIPEA, CH_2Cl_2	**4c**	87% yield

Table 4. Preparation of Pyrone by Effenberger Method



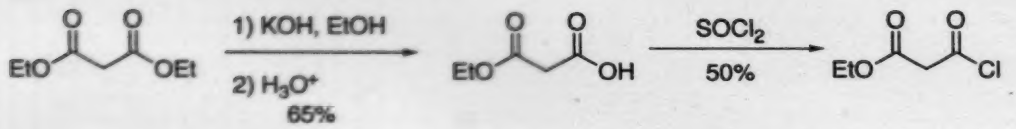
4a-c **5a-c** **5a'-c'**

entry	R	comments
1	TBDPS	**5a/5a'** (1:1), 44% yield
2	TBS	**5b/5b'** (1:1), 50% yield
3	MOM	**5c/5c'** (1:1) from crude ^{1}H-NMR



Scheme 3

An alternative route to make the desired 2-pyrone involves a two step sequence: (1) preparation of a diketone ester; (2) cyclization of the diketone ester by treatment with base. We first sought to perform the acylation on the protected α-hydroxy ketone, **4a**. Many acylation approaches were examined (Table 5). The acid chloride of ethyl malonate was prepared in a two step reaction. Controlled hydrolysis of diethyl malonate resulted in the monoacid. Treatment of the carboxylic acid with $SOCl_2$ resulted in an acyl chloride which was then purified by reduced-pressure distillation (Scheme 4).[10] Direct acylation on a lithium enolate failed (entry 1). Treatment of ketone **4a** with LDA and TMSCl resulted in a silyl enol ether, on which acylation in the presence of different Lewis acids was unsuccessful (entries 2 and 3). Enamine chemistry reported by Stork[11] was then examined for use in this reaction. Enamines were prepared by treatment of ketone **4a** with cyclic amines. Treatment of the pyrrolidine enamine with acid chloride and subsequent hydrolysis resulted in diketone ester **6** in a poor yield (entry 4). When the morpholine enamine was used, the desired diketone ester **6** was isolated in much better yield (entry 5). Two types of bases, NaOMe and DBU,[12,13] were used to induce cyclization of **6**. DBU was found to give product **7** in a synthetically useful 60% yield (Scheme 5).

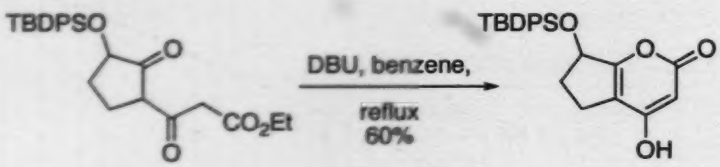


Scheme 4

Table 5. Preparation of Diketone Ester 6

4a **6**

entry	Conditions	comments
1	LDA, $ClCOCH_2CO_2Et$, -78°C	complex mixture
2	1) LDA, TMSCl, -78°C 2) $ClCOCH_2CO_2Et$, $ZnCl_2$	complex mixture
3	1) LDA, TMSCl, -78°C 2) $ClCOCH_2CO_2Et$, 5% $BiCl_3$-3NaI, CH_2Cl_2/Et_2O (9:1)	complex mixture
4	1) pyrrolidine, TsOH,benzene, 2) $ClCOCH_2CO_2Et$, Et_2O, -78°C → rt 3) H_3O^+	30% overall yield
5	1) morpholine, TsOH,benzene 2) $ClCOCH_2CO_2Et$, Et_2O, -78°C → rt 3) H_3O^+	75% overall yield

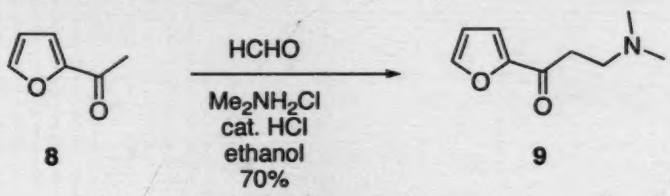


6 **7**

Scheme 5

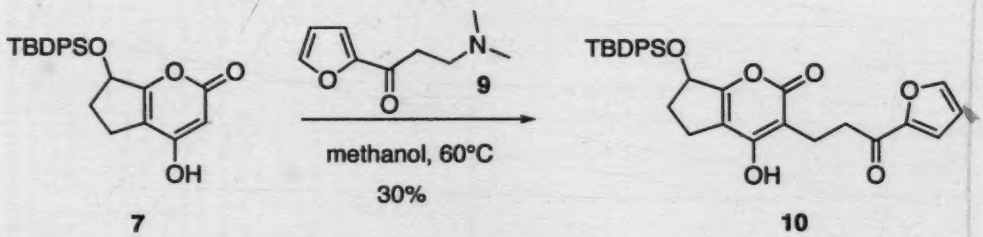
With pyrone **7** in hand, we attempted to do the coupling reaction with furan **9**, which can be easily prepared from 2-acetyl furan, **8**. Treatment of commercially available 2-acetyl furan under Mannich reaction conditions resulted in β-amino ketone **9** in good yield (Scheme 6).[14] Unfortunately, coupling of pyrone **7** and β-

amino ketone **9** did not provide **10** in synthetically useful yields.[15] After the investigation of different solvents and temperatures, the best outcome was a 30% yield of product **10** when the solution was heated in methanol at 60°C (Scheme 7). Mechanistically, β-amino ketone **9** is believed to first undergo elimination of dimethyl amine upon heating to generate an enone *in situ*. Conjugate addition of pyrone **7** to the enone resulted in coupling product **10**. Dimethyl amine generated during the reaction functions as a proton transfer reagent. In an attempt to improve the yield, we planned to use the enone directly instead of generating this reactive intermediate *in situ* (Table 6). The enone can be easily prepared from β-amino ketone **9** (Scheme 8).[16] Treatment of β-amino ketone **9** with methyl iodide resulted in a quaternary ammonium salt. Elimination of trimethylamine in the presence of sodium bicarbonate afforded the desired enone **11**. When the conjugate addition reaction was first carried out with the help of diethyl amine, poor results were obtained (entry 1 and 2). However, in the presence of potassium carbonate only the *O*-alkylation product was isolated (entry 3). Different conditions which used Lewis acids were examined since Michael addition reactions also can be catalyzed by Lewis acids. $ZnCl_2$ and $NiCl_2$ catalyzed conjugate addition afforded poor yields (entry 4 and 5). When $FeCl_3 \cdot 6H_2O$ was used as the catalyst, the yield was improved dramatically to 71% (entry 6). Iron (III) catalysis is a highly efficient alternative to base catalysis for the Michael reaction.[17]



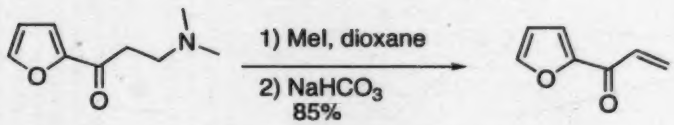
8 **9**

Scheme 6



7 **10**

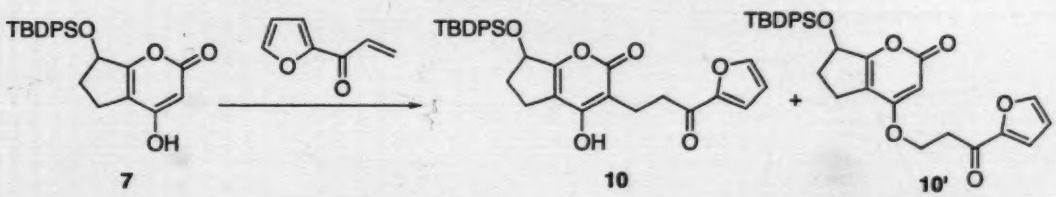
Scheme 7



9 11

Scheme 8

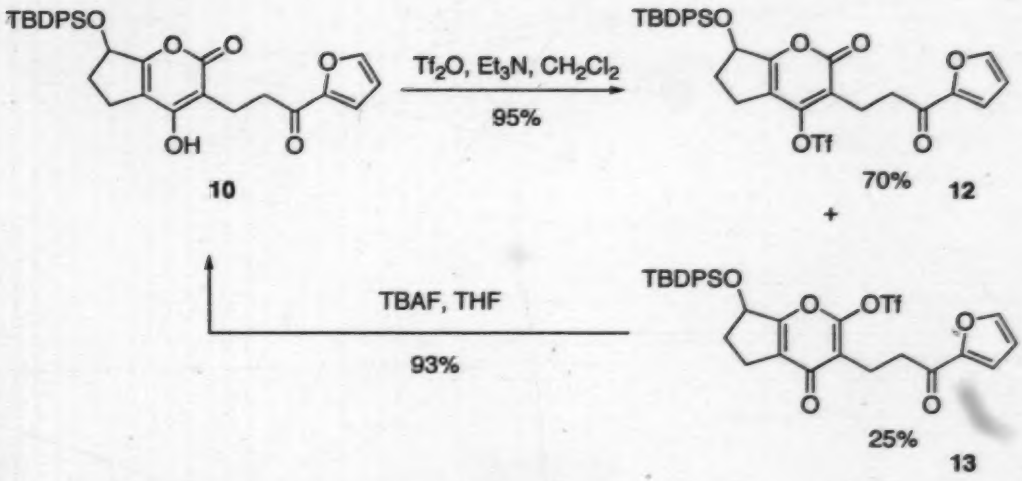
Table 6. Preparation of Pyrone Tethered with Furan



7 10 10'

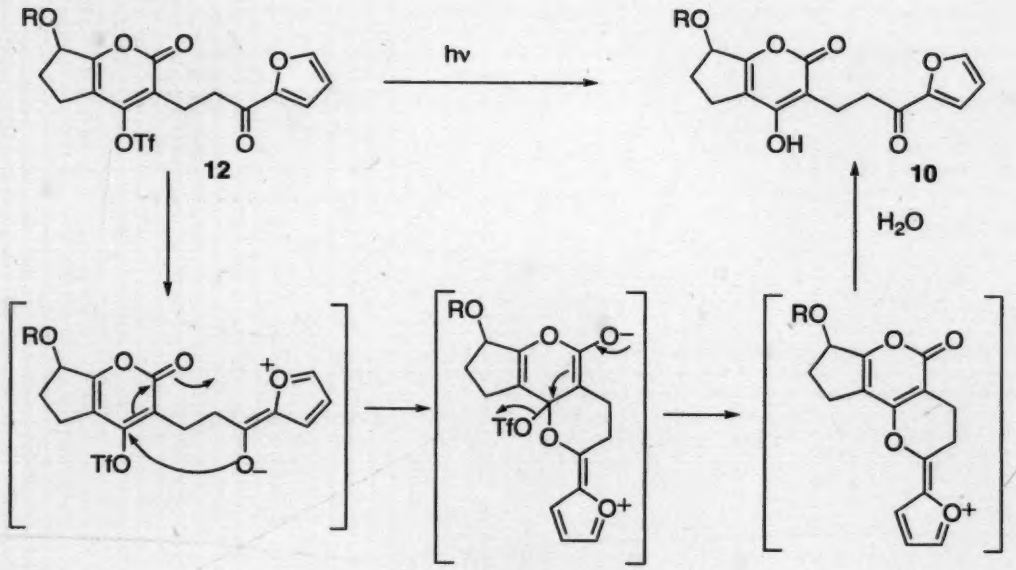
entry	conditions	comments
1	Et_2NH, CH_3CN	complex mixture; 20% of **10**
2	Et_2NH, THF	complex mixture; 20% of **10**
3	K_2CO_3, THF	only *O*-alkylation product **10'**
4	$ZnCl_2$, CH_2Cl_2	complex mixture
5	$NiCl_2$, CH_2Cl_2	slow reaction, complex mixture
6	$FeCl_3 \cdot 6H_2O$, $CHCl_3$	71% of **10**

Since deoxygenation at C-1 of the tricyclic skeleton is eventually required, the hydroxypyrone **10** was converted into the triflate **12** by treatment with triflic anhydride and triethylamine. Minor amounts of isomeric pyran-4-one **13** were also isolated in this reaction. The structures of the two products **12** and **13** were identified by the comparing UV absorption. Different bases such as Et_2NH, pyridine, and $i Pr_2EtN$ were examined, and all afforded similar results. Fortunately, the minor pyran-4-one **13** could be recycled upon treatment with tetrabutylammonium fluoride. This reaction proceeded very quickly and left the silyl group untouched. When the reaction was left for a longer period of time, the desilylated product was isolated (Scheme 9).



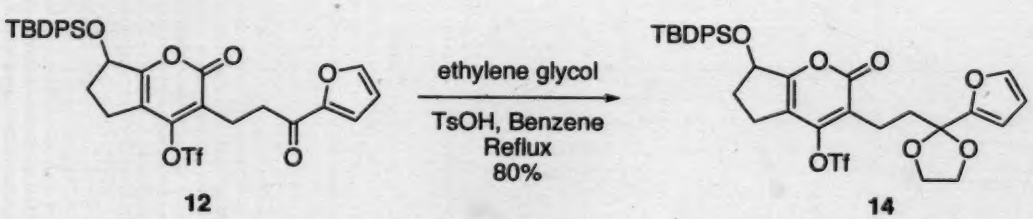
Scheme 9

Without ketalization of the isolated carbonyl group, irradiation of **12** in MeOH/H_2O with a Pyrex filter resulted in only desulfonated product **10** (Scheme 10). When **12** was protected as the ethylene ketal, [4+4]-photocycloaddition did occur. This observation suggested that the tethered carbonyl group must be involved in the desulfonation step. This phenomena was previously observed by Bender and West.[18] One proposed mechanism involved generation of a charge-separated intermediate upon irradiation. The ketone oxygen then participated in a Michael addition with the pyrone, followed by elimination of the triflate. Finally, hydrolysis would provide the hydroxy pyrone. The hydroxyl compoound **10** is stable under irradiation conditions so that no photocycloaddition products were observed. In order to allow the desired [4+4]-cycloadditions to occur, the carbonyl functionality must be protected.



Scheme 10

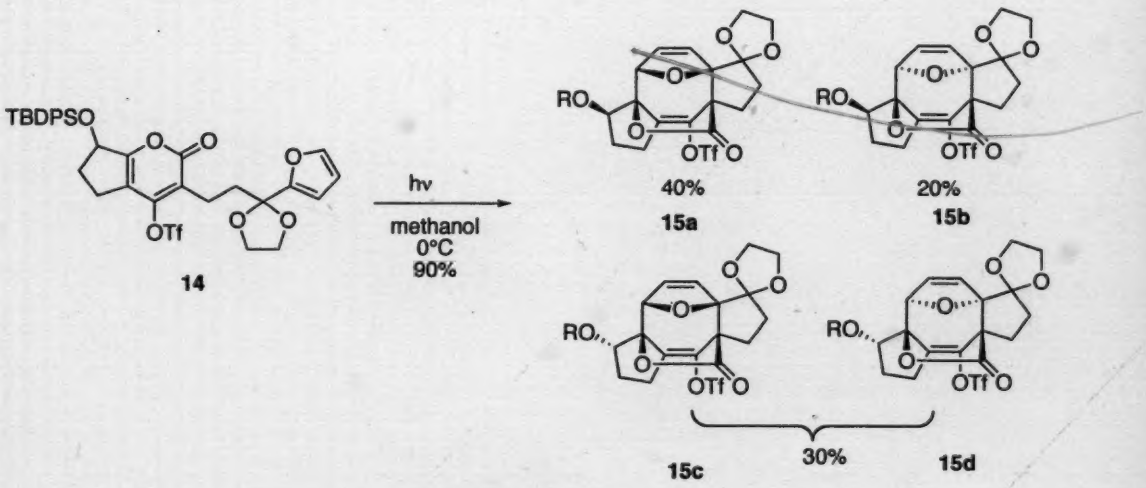
Treatment of triflate **12** with ethylene glycol and TsOH in benzene resulted in ketalization product **14**. This reaction was slow and took 2 days for consumption of starting material (Scheme 11).



Scheme 11

Irradiation of protected photosubstrate **14** in methanol afforded a mixture of four diastereomers: *endo* and *exo* cycloadducts **15a/15b** resulting from approach of the furan opposite to the OTBDPS group and *endo* and *exo* cycloadducts **15c/15d** resulting from furan delivery from the same face as the OTBDPS group (Scheme 12). The identity of the major pair of isomers was assumed to be **15a** and **15b**, based on the predicted approach of the furan from the less hindered face. This substrate is so reactive that photocycloaddition can even occur at -78°C in a short reaction time to

give the same ratio of products. *Endo* and *exo* in this context refers to the relative orientation of the two diene reactants in the [4+4]-cycloaddition transition state. The *endo* transition state places furan C-3 and C-4 over the internal carbons of the pyran-2-one diene system, leading to a product in which the lactone and ether bridges are *cis* in the newly formed cyclooctadiene. The *exo* transition state places furan C-3 and C-4 over the lactone moiety, leading to a product with the lactone and ether bridges *trans* disposed on the cyclooctadiene. For substrates such as **14** possessing a preexisting stereocenter, two *endo* and two *exo* products are possible, corresponding to approach of the furan from the same or the opposite face as the OR group (Figure 1).



Scheme 12

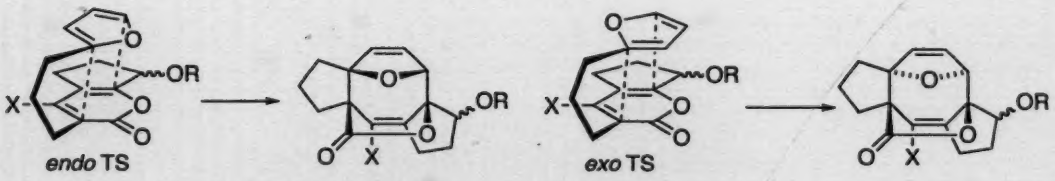
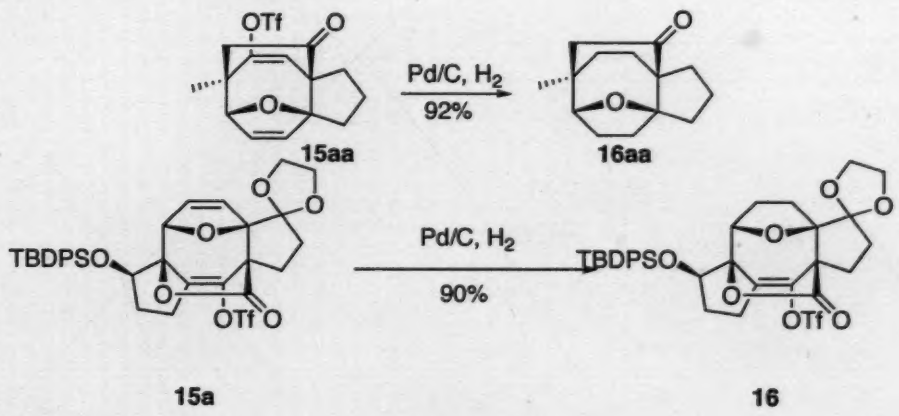


Figure 1. *endo* and *exo* Transition States

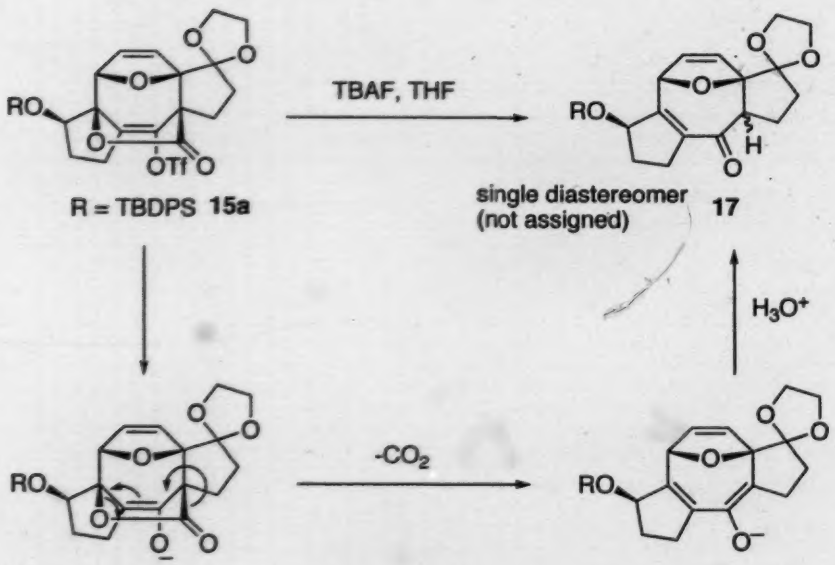
The major isomer **15a** was chosen to carry on to the next step. Based on the previous example reported in our group,[19] both the olefin and enol triflate were

anticipated to be reduced under hydrogenation with Pd/C (Scheme 13). Hydrogenation of **15aa** afforded fully reduced product **16aa** in our previous observation. Unfortunately, hydrogenation only provided the product **16** of olefin reduction even when subjected to high H_2 pressure (2000 psi). We have attributed this failure to the bulky TBDPS group since it appears to block the top face of the molecule and prevents hydrogen delivery to the enol triflate. Also the tetra-substituted enol triflate would be more difficult to reduce than the tri-substituted substrate in our previous studies.



Scheme 13

We decided to remove the TBDPS group before the hydrogenation reaction. Unfortunately, deprotection of TBDPS using TBAF gave the decarboxylation product **17** instead of the desired free secondary alcohol (Scheme 14). The decarboxylation was complete in 5 minutes. Since 1.1 equivalents of TBAF were used, the free alcohol derivative - after decarboxylation - could be formed when the reaction was left for a long time. We propose that the enol triflate is very labile under the TBAF conditions resulting in an enolate intermediate. The enolate could undergo decarboxylation to give a conjugated dienolate, which was protonated to afford a single isomer. The stereochemistry of that carbon has yet to be assigned. This observation of facile desulfonylation of enol triflate by TBAF was applied in the conversion of pyran-4-one **13** to pyran-2-one **12** as described earilier (Scheme 9).



Scheme 14

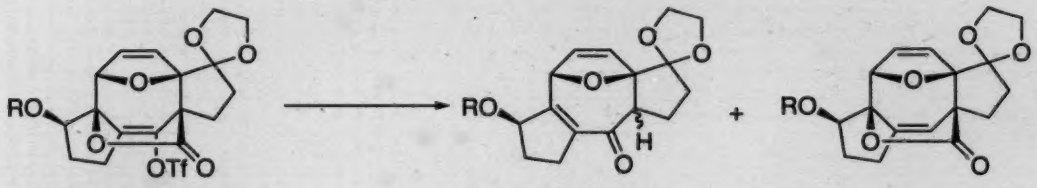
Due to the unexpected result from the attempted deprotection of the TBDPS group, we decided to first convert enol triflate **15a** into an olefin using the Stille reaction, before deprotection and hydrogenation. However, under two different sets of Stille reaction conditions,[20] only 5% of the desired olefin was isolated. The major product of this reaction was the decarboxylation product **17** (Table 7).

Since the vinyl triflate was problematic during further elaboration of the [4+4]-cycloadduct, we decided to replace the OTf with hydrogen *prior to* the photoreaction. To obtain this new substrate, a variety of hydride sources were investigated for the reduction of **14** (Table 8). When formic acid or tributyltin hydride were used as hydride sources, the 4-hydroxy-pyran-2-one **20** was obtained (entries 1 and 2). Based on these observations, the sulfur-oxygen bond seems to be very weak in this substrate. When catalytic hydrogenation was applied, only a small amount of the desired product could be obtained (entry 3). The other side products might come from the hydrogenation of the furan or pyrone moieties. Direct hydrogenation cannot be controlled by changing the reaction pressure. When the hydride source was switched to triethylsilane, two isolable products were identified as

the pyrone, **20**, and expected product, **19** (entry 4). Generally, under the standard Stille coupling conditions, LiCl is added to activate the reaction by exchange of the chloride for OTf. Because the vinyl triflate substrate was susceptible to nucleophilic attack, the addition of LiCl might result in the formation of the undesirable pyrone product. Without LiCl, only the desired product, **19**, was isolated (entry 5). This reaction is clean, high yielding and quick.

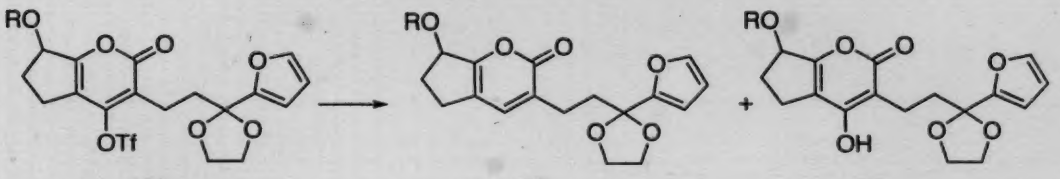
With this substrate in hand, we set out to examine its photochemical behavior using methanol as the solvent (Scheme 15). However, the initial results revealed relatively poor facial selectivity in the [4+4]-cycloaddition: two pairs of apparent *endo/exo* isomers were obtained in a disappointing ratio of 4:3. Based on previous studies on the photocycloaddition reaction, solvent has been shown to affect the outcome of the photoreaction. In this case, methanol could hydrogen bond to the carbonyl on the pyrone ring, and also acts as a polar solvent. We decided to examine aprotic and nonpolar solvents, like benzene and hexanes (Table 9). Irradiation of **19** in hexanes led to 7:1 facial selectivity compared with 4.5:1 facial selectivity in benzene. As a result, hexanes was the solvent used in subsequent experiments.

Table 7. Conversion of Enol Triflate to an Olefin by Stille Reaction



entry	conditions	comments
1	$Pd(OAc)_2$, HCOOH, Et_3N, PPh_3, DMF, 60°C	60% yield of **17** 5% yield of **18**
2	$Pd(PPh_3)_4$, Bu_3SnH, LiCl, THF, reflux	complex mixture

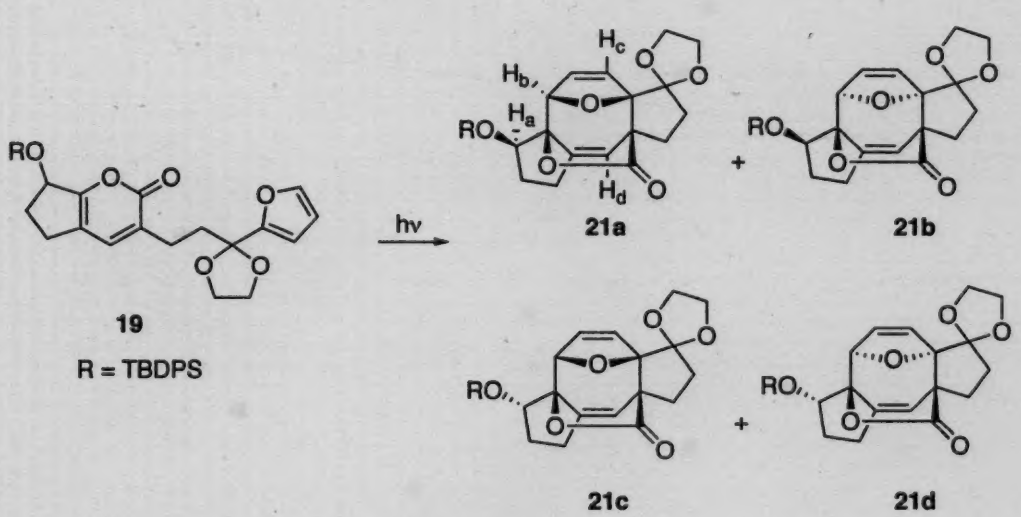
Table 8. Deoxygenation of Triflate by Stille Reaction



14 **19** **20**

R = TBDPS

entry	conditions	comments
1	$Pd(OAc)_2$, HCOOH, Et_3N, PPh_3, DMF, 60°C	pyrone **20** (65%)
2	$Pd(PPh_3)_4$, Bu_3SnH, LiCl, THF, reflux	complex mixture
3	Pd/C, H_2, Methanol	complex mixture
4	$Pd(PPh_3)_4$, Et_3SiH , LiCl, DMF, 60°C	**19** : **20** (4:1), 82% yield
5	$Pd(PPh_3)_4$, Et_3SiH, DMF, 60°C	92% yield of **19**



19

R = TBDPS

21a **21b**

21c **21d**

Scheme 15

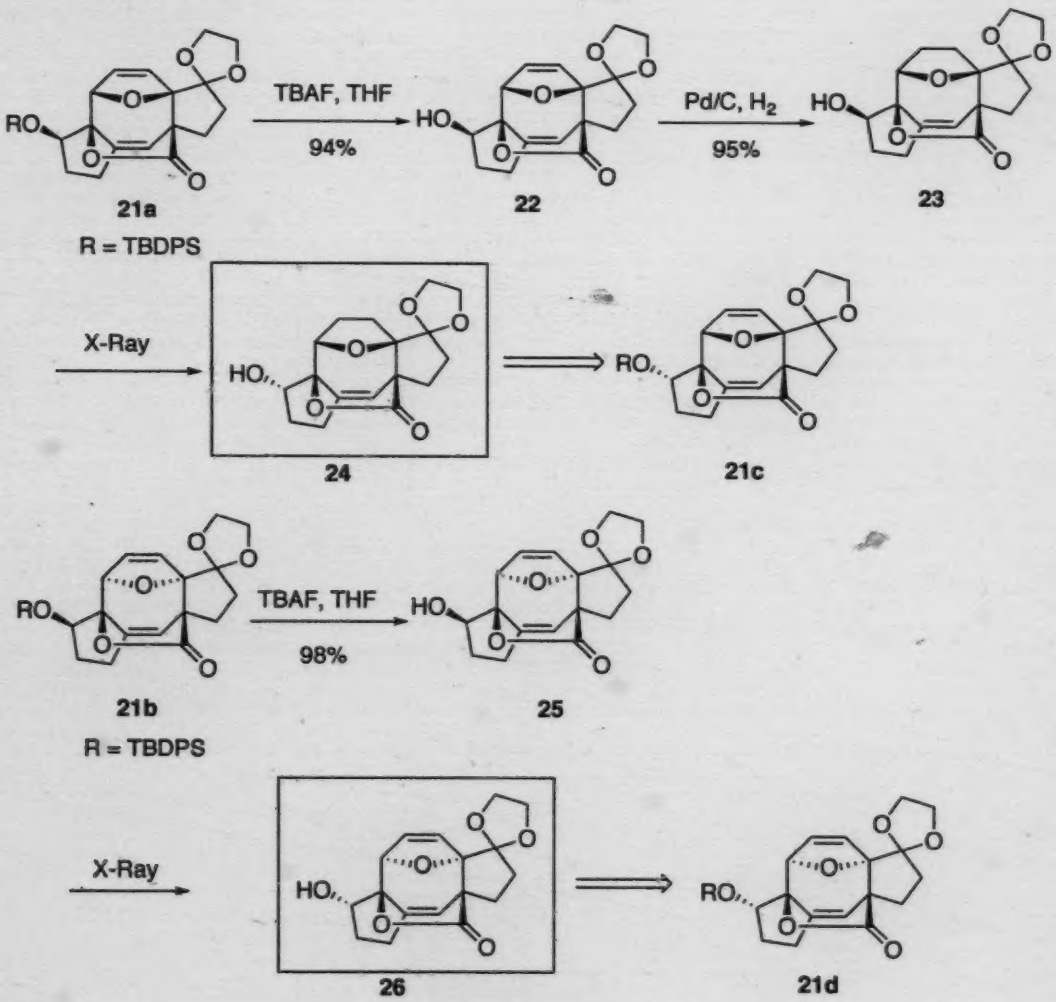
Table 9. Solvent Effects in the Photocyclization

	Major (endo) **21a**	Major (exo) **21b**	Minor (endo) **21c**	Minor (exo) **21d**
MeOH	3.7	1	1.5	2.1
Benzene	2.0	2.5	0	1
Hexanes	3.7	3.3	0	1

The stereochemistry of two the major isomers was tentatively assigned by TROESY. When the furan approached the pyrone from the opposite face of OTBDPS, the resulting isomers should display an NOE effect between the H_a and H_b (**21a** in Scheme 15). For the *endo* isomer **21a**, H_c and H_d should have an NOE correlation. On the TROESY spectrum, these predicted interactions were observed. However, in order to make unequivocal assignment, crystalline derivatives of the two major isomers were sought (Scheme 16). Deprotection of **21a** with TBAF gave the free alcohol **22**. Reduction of the disubstituted double bond of **22** by hydrogenation afforded the solid **23**, which was submitted for X-ray analysis (Figure 2).[21] To our surprise, this structure proved to be tricyclic compound **24**, which would be derived from the cycloadduct **21c**. The crystal structure of **25** was also obtained (Figure 3).[21] These two crystal structures showed that our tentative facial assignment was wrong, but the *endo* and *exo* assignment was correct. The major isomers from irradiation were a result of furan approach from the *same* face as the bulky OTBDPS group.

This unexpected diastereoselectivity prompted us to examine the effects of the alcohol protecting group R and ring substituent X. Substrates **27, 28, 29** were easily prepared by deprotection of **19** with TBAF, followed by treatment with the appropriate reagents (TBDMSCl/imidazole or Ac_2O/Et_3N) (Scheme 17). Following irradiation, the resulting photocycloadducts were deprotected and assigned as **30a, 30b, 30c, 30d**. In all cases, overall photocycloaddition yields were good and isomers **30a** and **30b** were the major products. However, the relative amounts of minor isomers increased as the size of the R group decreased. Triflate-substituted

compound **14** gave comparable results. In this case, the major photoproducts were assigned by comparison with **21c** and **21d** after reductive removal of the triflate ($Pd(PPh_3)_4/Bu_3SnH$).



Scheme 16

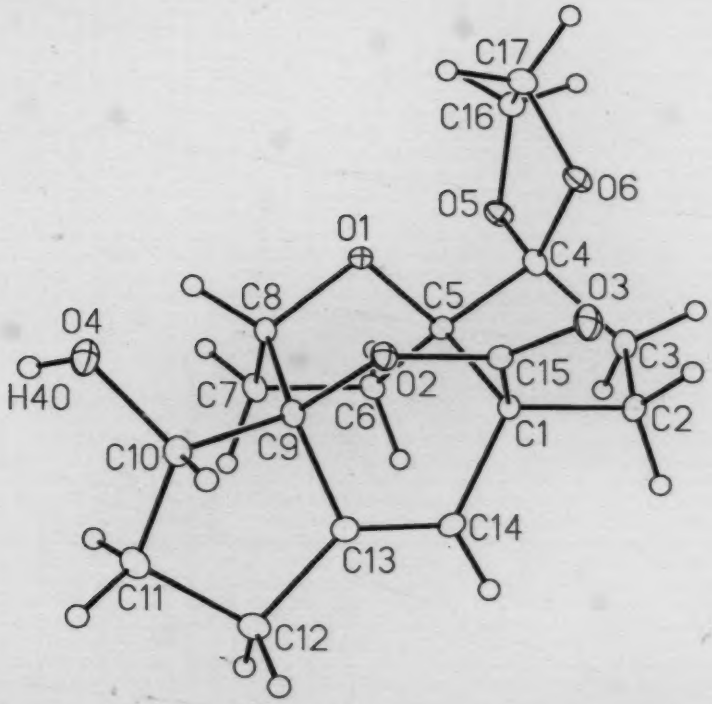


Figure 2. X-Ray Structure of Compound 24 (See Appendix C)

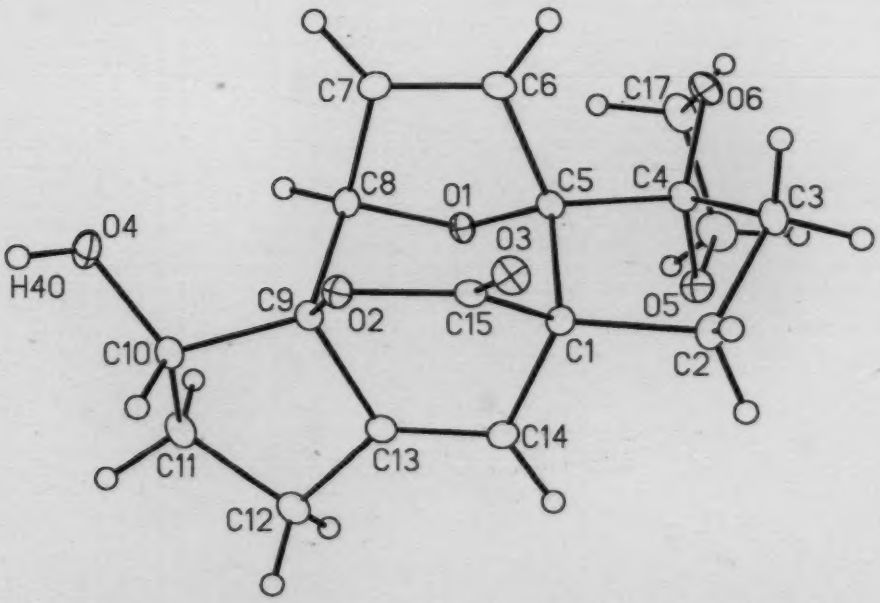
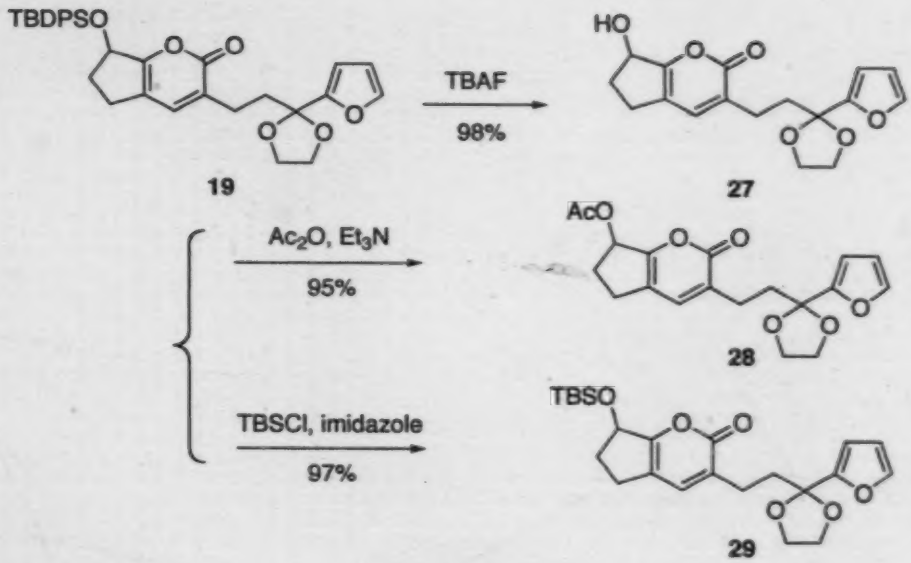
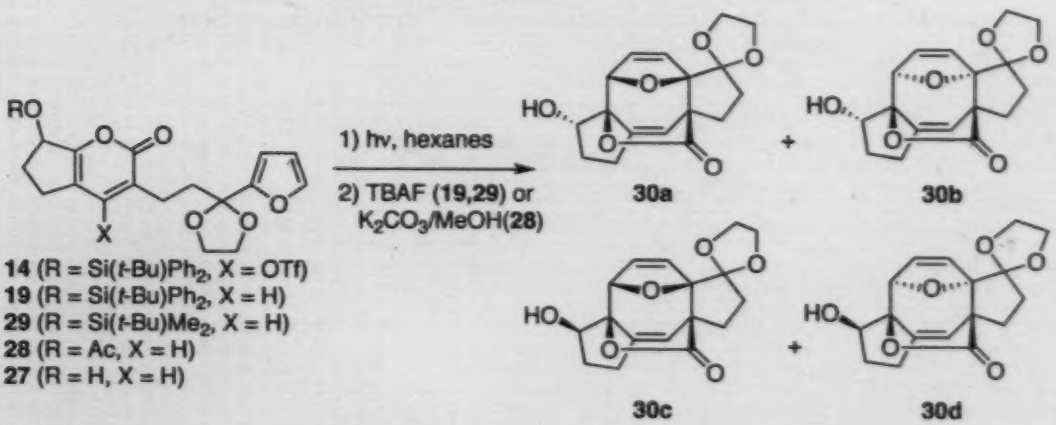


Figure 3. X-Ray Structure of Compound 26 (See Appendix D)



Scheme 17

Table 10. Photocycloaddition with Different Protecting Group



14 (R = Si(*t*-Bu)Ph_2, X = OTf)
19 (R = Si(*t*-Bu)Ph_2, X = H)
29 (R = Si(*t*-Bu)Me_2, X = H)
28 (R = Ac, X = H)
27 (R = H, X = H)

entry	substrate	overall yield (%)	ratio **30a:30b:30c:30d**	ratio **(30a+30b):(30c+30d)**
1	**19**	90	3.7:3.3:0:1.0	7.0:1
2	**29**	75	10.0:9.4:1.0:2.4	5.7:1
3	**28**	70	3.1:3.8:1.0:1.9	2.3:1
4	**27**	84	4.0:3.5:1.0:2.0	2.5:1
5	**14**	95	8.3:2.7:1.5:1.0	4.4:1

We expected that the bulky TBDPS group in **19** would block the same face as the protecting group, so that furan would preferentially approach the pyrone from the opposite face as TBDPS. However, the X-ray results prove our assumption that isomers **21a** and **21b** would be the major isomers is wrong. It seems that this simple steric effect is not the dominant factor of the facial selectivity during the cycloaddition. To explain this unexpected facial selectivity, one possibility is still the steric effect. In the conformers A and B (Figure 4), a silyl ether and a hydrogen atom occupy pseudoequatorial and pseudoaxial positions, respectively. The pseudoaxial hydrogen atom could hinder the approach of furan from the same face as hydrogen atom. Another possibility is a product development control argument by a later transition state. When furan approaches pyrone from the opposite face of the OR group, the lactone bridge could cause a eclipsing interaction with OR group (conformer C and D). On the contrary, when furan comes from the same face as OR group, the lactone would move away from OR group. However this surprising result does not affect our original synthetic plan, since this carbon center that is assigned wrong would become a sp^2 center untimately. We just need to start with the other enantiomer of 2-hydroxycyclopentanone. In the meantime, the two major diastereomers in the racemic series were carried on to examine the feasibility of the later steps in the synthetic plan.

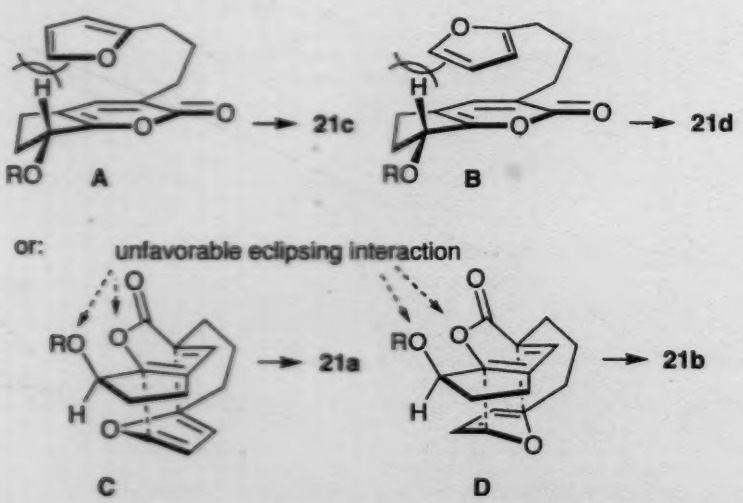
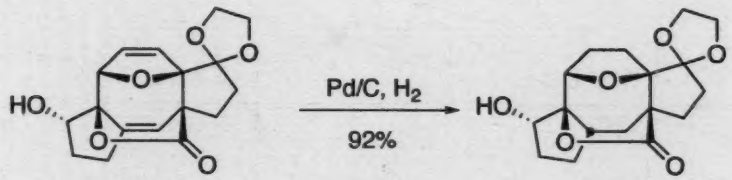


Figure 4. Steric Effect and Later Transition State

Hydrogenation of intermediate **30a** over palladium on carbon gave a single reduction product **31** (Scheme 18). Molecular models strongly suggest that only the top face of **30a** should be accessible, so we tentatively assign the stereochemistry as shown.



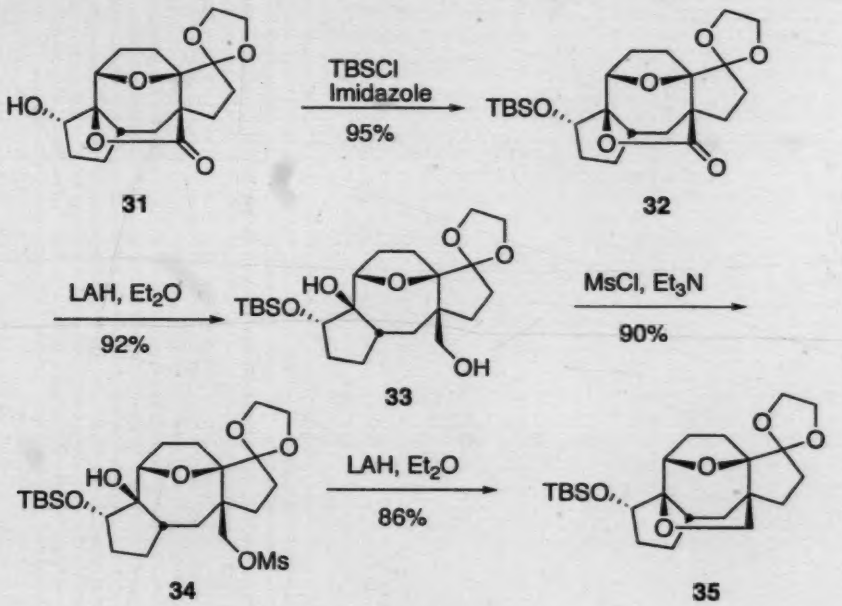
30a **31**

Scheme 18

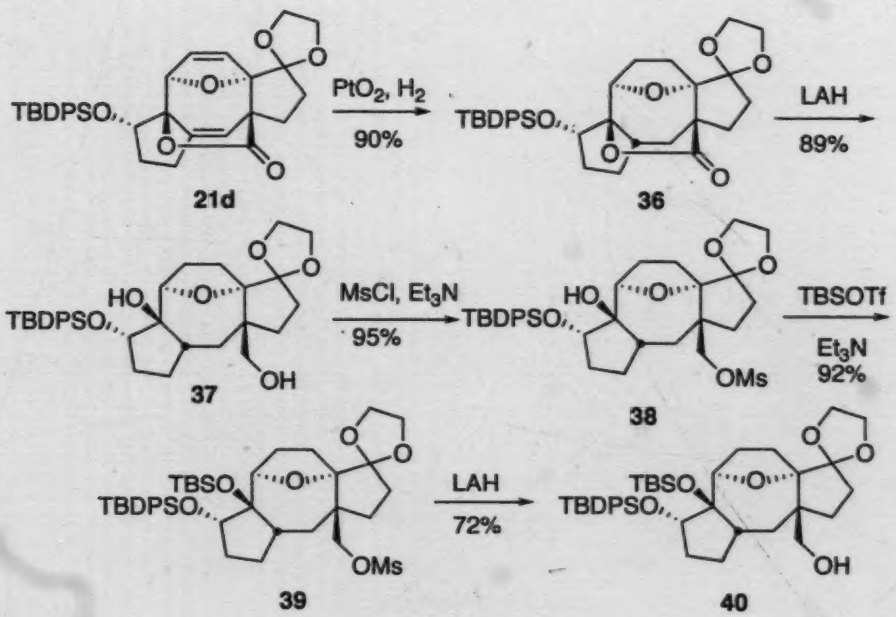
The resulting product **31** was then protected with a TBS group to give **32** in good yield. The bridging lactone was cleaved by treatment with lithium aluminium hydride to afford diol **33**. The next challenge was the deoxygenation of the primary alcohol. The first strategy utilized S_N2 displacement.[22] Treatment of diol **33** with MsCl and triethylamine resulted in **34**. These conditions allowed selective functionalization of the primary hydroxyl group. Unfortunately, intramolecular displacement occurred to give product **35** when the substrate was treated with lithium aluminium hydride. Apparently, the tertiary hydroxyl group was deprotonated upon treatment with $LiAlH_4$ and proceeded to displace the OMs since they were in close proximity (Scheme 19).

Due to the interference of the tertiary hydroxyl group, we want to protect it with a TBS group. Here we used *exo* isomer **21d** to test this approach. We found treatment of **21d** with PtO_2 could result in fully reduced product **36**. Opening of the bridging lactone by lithium aluminium hydride afforded diol **37**. Treatment of diol **37** with MsCl and triethylamine resulted in **38**, which was then protected with a TBS group to give **39**. Unfortunately, treatment of this substrate with LAH did not give the desired product either. The isolated product was tentatively identified as the primary alcohol **40**. The angular methylene carbon, which is neopentyl, is very

sterically hindered so that even the smallest nucleophile cannot access it, allowing simple desulfonylation to occur as the major pathway.

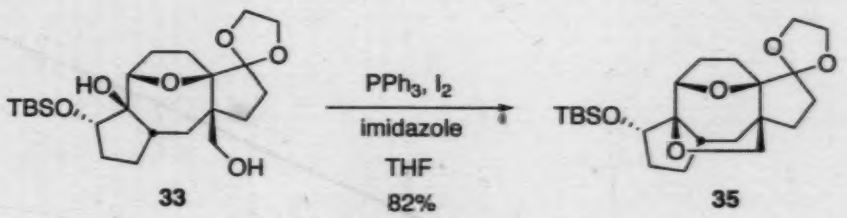


Scheme 19



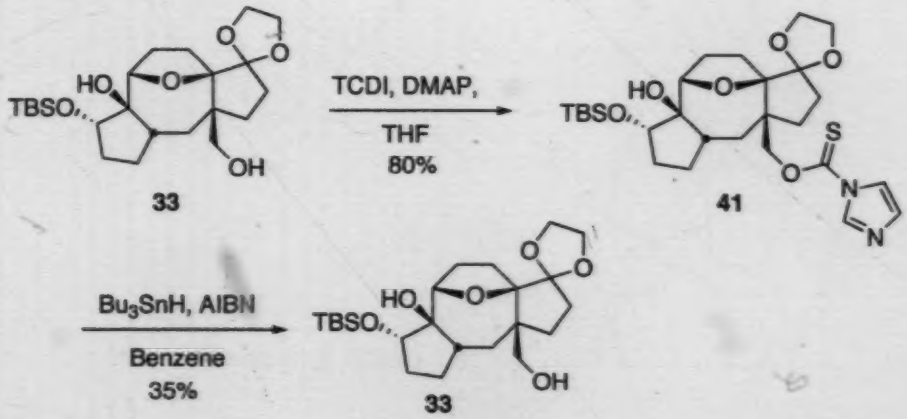
Scheme 20

The second attempted strategy involved a radical reaction. First, we planned to convert the primary hydroxyl group into an iodide by treatment with I_2 and triphenylphosphine,[23] then perform a radical reduction. Unfortunately, the angular hydroxyl group still affected this reaction by intramolecular displacement of the resulting phosphonium intermediate to provide the cyclic product **35** (Scheme 21).



Scheme 21

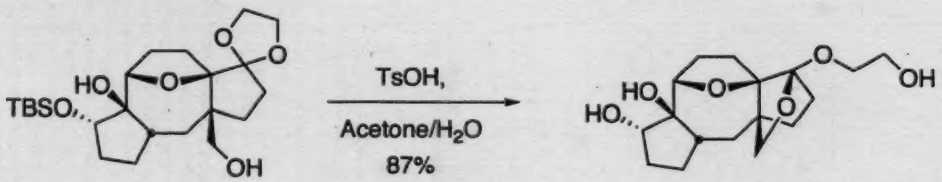
Barton deoxygenation was then investigated. Treatment of primary alcohol **33** with thiocarbonyl diimidazole resulted in Barton ester **41**.[24] Treatment of Barton ester **41** under the standard radical conditions did not afford the deoxygenation product. Small quantities of the starting alcohol can be recovered from this messy reaction (Scheme 22).



Scheme 22

Because of the failure of the previously outlined two strategies, we decided to change the conformation of substrate **33** by cleavage of the bridging ether and then

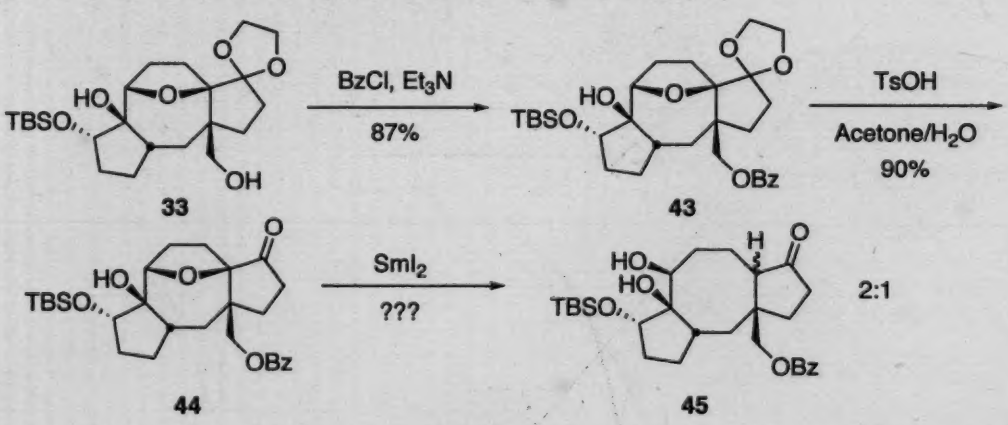
protection of the 1,2-diol as a ketal. In order to cleave the ether, initial removal of the ketal protecting group was required. Treatment of **33** under acidic conditions resulted in compound **42** (Scheme 23). An initially formed oxocarbenium ion was trapped intramolecularly by the primary hydroxyl group to generate the undesired product. Meanwhile, the TBS protecting group was removed by TsOH, which was added in excess. So this primary alcohol must be protected or removed before the ketal deprotection can happen.



33 **42**

Scheme 23

Subsequently, we decided to protect the primary hydroxyl group before deprotection of the ketal. Treatment of diol **33** with benzoyl chloride and triethylamine resulted in compound **43**. Deprotection of the ketal using acetone and water in the presence of TsOH gave the desired ketone **44**. Treatment of this substrate with SmI_2 resulted in the cleavage products **45** in a 2:1 ratio of epimers (Scheme 24).[25] The isomers, presumed to be epimeric at the bridgehead position, have not been isolated and fully identified. The tentative assignment was only based on the crude proton NMR spectrum and mass spectral analysis.

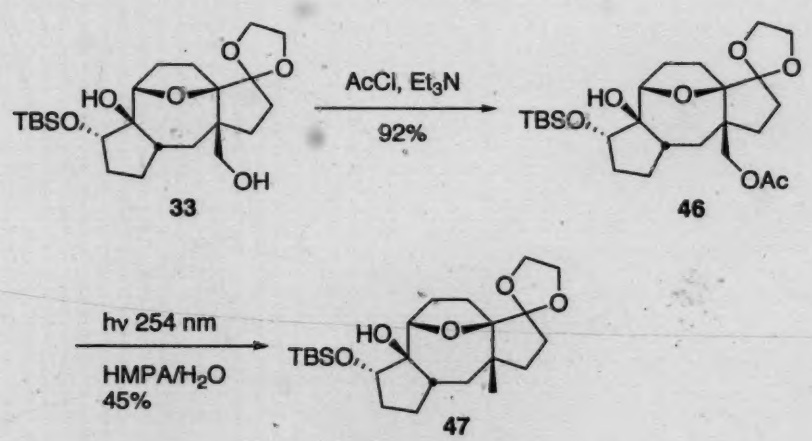


33 **43**

44 **45**

Scheme 24

Another method to do the deoxygenation would be photoreduction of an acetate. Treatment of diol **33** with acetyl chloride and triethylamine resulted in compound **46**. Fortunately, simple photoreduction of the acetate **46** in HMPA/H_2O[26] furnished **47**. This photolysis of acetate is mild and clean.



Scheme 25

2.3 Conclusion and Future Work

In our synthetic studies, we used a novel strategy for the stereoselective construction of functionalized 5-8-5 tricyclic systems using a crossed intramolecular [4+4]-photocycloaddition of pyran-2-ones. By this route, complex polycycles that are suitable intermediates for the synthesis of traversianal and members of the fusicoccin family of fungal metabolites are available in 7–9 steps from 2-siloxycyclopentanone **4a**. By inclusion of a preexisting stereocenter on a cyclopentene ring fused to the pyran-2-one, facial selectivities of up to 7:1 are obtained in the photocycloaddition reaction. Notably, the major isomers arise from approach of the furan trap from the *same* face as the bulky substituent.

Several interesting reactions have been developed for pyran-2-one chemistry. Fused bicyclic pyran-2-ones **10** with pendant furan side chains were prepared *via* $FeCl_3$-catalyzed Michael addition. The addition is high yielding and conditions are

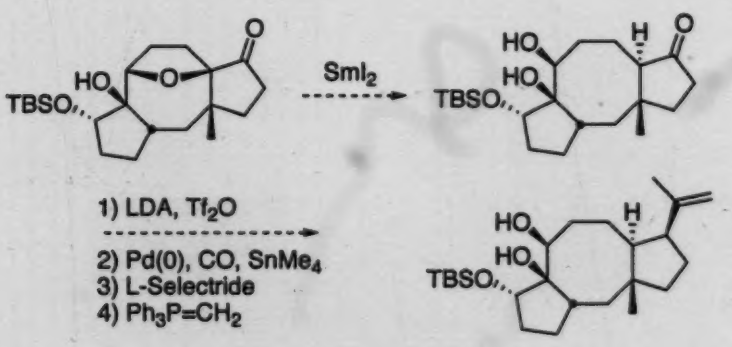
mild and water tolerant. To our knowledge, alkylation on the C-3 position of pyran-2-ones by $FeCl_3$-catalyzed Michael addition has not been reported in the literature.

Minor amounts of the isomeric pyran-4-one **13** formed in the sulfonylation reaction of **10** could be recycled by conversion to **10** upon treatment with tetrabutylammonium fluoride.

Reductive removal of the triflate of **14** by using $Pd(PPh_3)_4$ as the catalyst and Et_3SiH as the hydride source gave deoxygenated substrate **19**. LiCl has typically been used in the simple Stille reaction; however, it was found that this particular reaction only proceeded in the absence of LiCl to give a single product.

After many failed approaches to the deoxygenation of **33**, photolysis of acetate was finally found to give clean deoxygenation product **47** very efficiently.

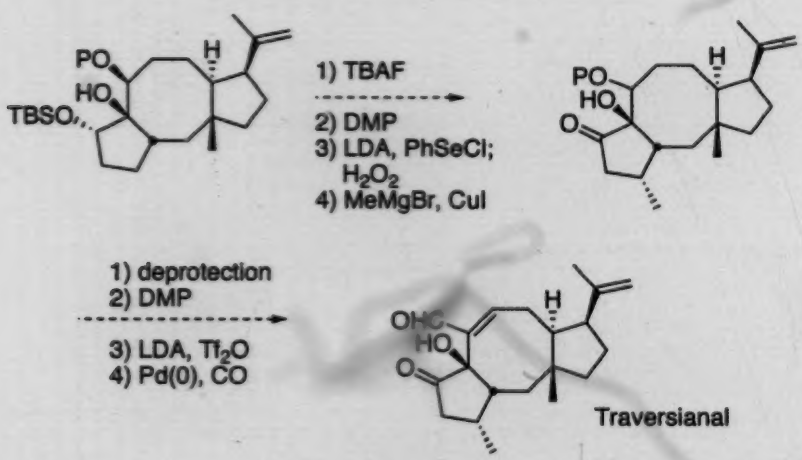
To complete the total synthesis of traversianal, there are still some problems that need to be solved, such as opening of bridging ether and installation of isopropenyl group. According to the initial result from SmI_2 shown in Scheme 24, it is very likely that the ether bridge could be opened by SmI_2. The isopropenyl group can be furnished by the following sequence of steps: conversion of ketone to enol triflate, Stille coupling, conjugate reduction of the enone and Wittig reaction (Scheme 26).



Scheme 26

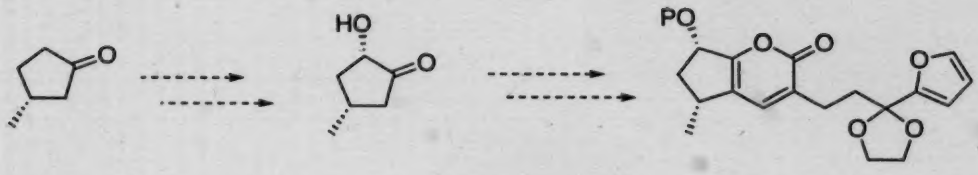
The next thing that needs to be done is the installation of methyl group to the β-postion of OTBS group. To install the methyl group, a sequence of three steps could be used: oxdition of alcohol to ketone, conversion of ketone to the enone and

conjugate addition to the enone with methyl cuprate. To establish the stereochemistry center in the conjugate addition step, the methyl group should attack the enone from the bottom face. However, based on the conformation of cis-5-8 ring system, the methyl group is more likely to deliver from the top face to give the opposite stereochemistry. If that happens, we need to make the enone again and then do the conjugate reduction with L-Selectride to invert the methyl group. That will take several more steps to accomplish this target. The last job is to modify the secondary alcohol to give unsaturated aldehyde. To accomplish this, the following sequence could be applied: oxidation of alcohol to the ketone, conversion of ketone to the enol triflate and Stille coupling with carbon monoxide (Scheme 27).



Scheme 27

To avoid this problem of the methyl group, we can consider incorporating the cyclopentane methyl group earlier in the sequence. Also based on the observation of racemic model, we need to start with the enantiomer of the starting hydroxyketone to control the real stereochemistry. Since we want to synthesize the real natural product not the racemic mixture, we can start with chiral 3-methyl cyclopentanone for the total synthesis of *Traversianal* (Scheme 28).

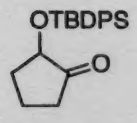


Scheme 28

2.4 Experimental

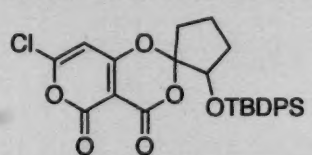
The copies of selected proton and carbon NMR spectra could be found in Appendix A **General Information**. Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran, diethylether and benzene from sodium/benzophenone ketyl, toluene from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.23 ppm). Infrared (IR) spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. Mass spectra were determined on a PerSeptive Biosystems Mariner high-resolution electrospray positive ion mode spectrometer (ESI) or on a Kratos Analytical MS-50 (EI). Elemental analyses were obtained at the University of Alberta on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

Standard conditions for irradiation: the substrate was dissolved in the appropriate solvent in a Pyrex vessel. After degassing for 30 min with N_2, the reaction was irradiated (450-W Hanovia medium-pressure Hg lamp) until starting material was consumed by 3 h. The reaction vessel was 20 cm away from the light souce.



4a

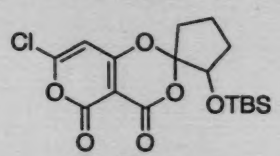
Preparation of 4a. 2-Hydroxycyclopentanone[8] (3.00 g, 30.0 mmol) was dissolved in DMF (30 mL) followed by the addition of imidazole (4.08 g, 60.0 mmol) and *tert*-butylchlorodiphenylsilane (11.7 mL, 45.0 mmol). The solution was stirred at room temperature for 3 h before dilution with ether (60 mL). The organic layer was washed with water (2 x 30 mL), brine (20 mL), and dried over $MgSO_4$. The solvent was removed by reduced pressure and the crude product was purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to yield 9.93 g (98% yield) of ketone **3a** as a colorless oil: R_f 0.45 (5:1 hexanes/EtOAc); IR (thin film) 1756, 1589, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.68 (m, 4H), 7.42-7.38 (m, 6H), 3.97 (dd, 1H, J = 7.9, 10.9 Hz), 2.23-2.12 (m, 2H), 2.02-1.96 (m, 1H), 1.92-1.84 (m, 1H), 1.80-1.70 (m, 1H), 1.61-1.45 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 218.0, 137.1, 136.9, 135.0, 134.3, 131.0, 130.9, 128.8, 128.7, 77.9, 35.5, 33.1, 27.4, 20.1, 17.4; HRMS (ESI) calcd for $C_{21}H_{26}O_2NaSi$ ($[M•Na]^+$) 361.1600, found 361.1603. Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.81; H, 7.73.



5a

Preparation of 5a. To a solution of LDA (3.3 mmol) in THF (15 mL) was added **4a** (1.0 g, 3.0 mmol) at -78°C. After 1 h, chlorotrimethylsilane (0.42 mL, 3.3 mmol) was added. The solution was washed with water (20 mL) and dried over $MgSO_4$ to provide crude silyl enol ether. To the resulting silyl enol ether of **4a** (0.36g, 0.89 mmol) in diethyl ether (5 mL) at -20°C was added malonyl dichloride (62 mg, 0.44 mmol) in diethyl ether (1 mL) dropwise. After 2 h, the reaction was quenched with water (5 mL) and extracted with diethyl ether (20 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to give two diastereoisomers (100 mg, 44% yield), one isomer

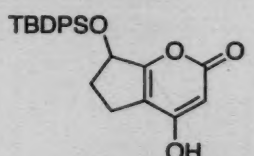
was fully characterized: R_f 0.33 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.52 (m, 4H), 7.42-7.32 (m, 6H), 5.82 (s, 1H), 4.24-4.20 (m, 1H), 2.24-2.18 (m, 1H), 2.08-2.00 (m, 1H), 1.86-1.66 (m, 2H), 1.66-1.58 (m, 1H), 1.52-1.42 (m, 1H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, CD_3Cl) δ 172.2, 157.0, 155.4, 154.5, 136.0, 135.7, 133.0, 132.5, 130.1, 130.0, 127.9, 127.6, 115.0, 99.0, 91.6, 78.9, 33.7, 30.4, 26.6, 19.0, 16.6; HRMS (ESI) calcd for $C_{27}H_{28}O_6SiCl$ ($[M•H]^+$) 511.1338, found 511.1342.



5b

Preparation of 5b. The previously outlined procedure was used to give two isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 4.20-4.18 (m, 1H), 2.28-2.10 (m, 2H), 2.00-1.80 (m, 3H), 1.74-1.62 (m, 1H), 0.78 (s, 9H), 0.00 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (100 MHz, CD_3Cl) δ 172.1, 157.0, 155.4, 154.5, 115.0, 99.0, 92.3, 78.4, 33.8, 31.2, 25.4, 17.8, 16.9, -4.8, -5.2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.22-4.18 (m, 1H), 2.28-2.10 (m, 2H), 2.16-2.00 (m, 1H), 1.88-1.82 (m, 1H), 1.78-1.62 (m, 2H), 0.78 (s, 9H), 0.02 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (100 MHz, CD_3Cl) δ 173.5, 157.4, 155.4, 154.6, 115.3, 99.4, 91.7, 77.3, 34.0, 31.5, 25.3, 17.6, 17.2, -4.9, -5.2.

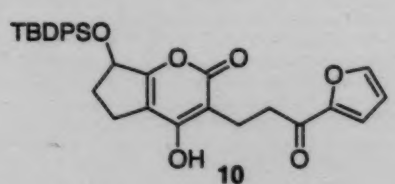


7

Preparation of 7. To a solution of ketone **4a** (6.00 g, 17.8 mmol) in benzene (50 mL) was added morpholine (1.70 mL, 19.5 mmol) and *p*-toluenesulfonic acid monohydrate (336 mg, 1.77 mmol). The reaction mixture was refluxed under a Dean-Stark trap until no further separation of water was observed. The solvent was removed by reduced pressure, the residue was redissolved in 50 mL diethyl ether and cooled to -78 °C (dry ice with acetone). Ethyl 3-chloro-3-oxopropanoate (1.78 mL, 14.2 mmol) (available from Aldrich) was then added dropwise over 30 min by syringe pump. The mixture was slowly warmed to room temperature and stirred for

12 h. Water (20 mL) was added and the mixture was stirred for 2 h. The phases were separated and the ethereal layer was washed with brine (30 mL) and dried over $MgSO_4$. The solvent was evaporated to afford a viscous liquid. The residue was purified by column chromatography (silica gel; hexanes/EtOAc 7:1) to afford 4.83 g (75% yield) of the desired diketo ester **6** as a pale red oil: R_f 0.34 (5:1 hexanes/EtOAc); IR (thin film) 1741, 1674, 1644, 1615, 1589, 1472, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.40 (br s, 1H), 7.82-7.65 (m, 4H), 7.48-7.36 (m, 6H), 4.48 (dd, 1H, J = 8.0, 9.1 Hz), 4.23 (q, 2H, J = 7.1 Hz), 3.32 (s, 2H), 2.47-2.41 (m, 1H), 2.27-2.22 (m, 1H), 2.08-2.03 (m, 1H), 1.84-1.79 (m, 1H), 1.30 (t, 3H, J = 7.1 Hz), 1.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 176.4, 167.2, 135.97, 135.82, 133.87, 133.0, 129.9, 129.8, 127.7, 127.6, 109.2, 75.7, 61.5, 41.9, 31.2, 26.7, 21.7, 19.3, 14.1; HRMS (ESI) calcd for $C_{26}H_{32}O_5NaSi$ ($[M•Na]^+$) 475.1911, found 475.1916.

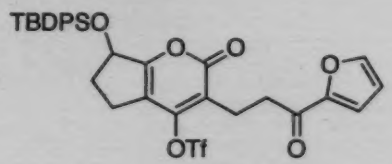
The diketo ester **6** (610 mg, 1.35 mmol) was dissolved in benzene (10 mL) and DBU (0.40 mL, 2.70 mmol) was added. The solution was refluxed for 5 h before dilution with dichloromethane (40 mL). The organic phase was washed with 1N HCl (2 x 10 mL), brine (10 mL), and dried over $MgSO_4$. The solvent was evaporated by reduced pressure and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 1:2) to yield 329 mg (60%) of pyrone **7** as a pale yellow oil: R_f 0.20 (1:1 hexanes/EtOAc); IR (thin film) 3300–2500, 1728, 1682, 1633, 1564 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.52 (br s, 1H), 7.80-7.74 (m, 4H), 7.46-7.38 (m, 6H), 5.74 (s, 1H), 5.02 (t, 1H, J = 6.2 Hz), 2.78-2.75 (m, 1H), 2.41-2.39 (m, 1H), 2.14-2.10 (m, 1H), 1.94-1.98 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.3, 170.0, 165.0, 137.0, 136.97, 134.88, 134.3, 131.08, 131.01, 128.84, 128.81, 115.0, 90.5, 75.8, 32.9, 27.4, 23.4, 20.0; HRMS (ESI) calcd for $C_{24}H_{26}O_4NaSi$ ($[M•Na]^+$) 429.1492, found 429.1491. Anal. Calcd for $C_{24}H_{26}O_4Si$: C, 70.90; H, 6.45. Found: C, 70.69; H, 6.54.



10

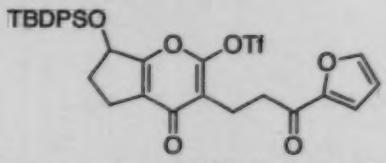
Preparation of 10. To a solution of pyrone **7** (260 mg, 0.64 mmol) in chloroform (2 mL) was added ferric chloride hexahydrate (17.3 mg, 0.064 mmol) and 1-(furan-2-yl)prop-2-en-1-one (93.7 mg, 0.77 mmol). The mixture was stirred at room temperature for 6 h. The solvent was then removed by reduced pressure to provide an oil, which was purified by column chromatography (silica gel; hexanes/EtOAc 2:1) to afford 240 mg (71% yield) of Michael adduct **10** as a pale yellow oil (along with 23 mg (9% yield) recovered **7**): R_f 0.43 (2:1 hexanes/ EtOAc); IR (thin film) 3300–2500, 1736, 1702, 1677, 1585, 1569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.78-7.70 (m, 4H), 7.68 (dd, 1H, J = 0.8, 1.7 Hz), 7.41-7.31 (m, 6H), 7.33 (dd, 1H, J = 0.8, 3.7 Hz), 6.60 (dd, 1H, J = 1.7, 3.7 Hz), 4.99-4.98 (m, 1H), 3.35-3.34 (m, 2H), 2.82-2.79 (m, 2H), 2.72-2.65 (m, 1H), 2.41-2.38 (m, 1H), 2.07-2.02 (m, 1H), 1.88-1.82 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 166.4, 164.35, 160.8, 151.8, 147.7, 136.0, 135.8, 134.0, 133.1, 129.72, 129.69, 127.62, 127.59, 119.4, 113.6, 112.7, 103.0, 74.4, 37.3, 31.7, 26.9, 22.9, 19.2, 16.9; HRMS (ESI) calcd for $C_{31}H_{32}O_6NaSi$ ($[M•Na]^+$) 551.1860, found 551.1864.

Preparation of 12 and 13. Compound **10** (560 mg, 1.06 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (0.18 mL, 1.27 mmol) was added, followed by triflic anhydride (0.20 mL, 1.2 mmol), which was added by syringe pump (10 μL/min). After the addition was complete, the mixture was stirred for another 10 min before the reaction was quenched with NH_4Cl (5 mL). The mixture was extracted with ethyl acetate (2 x 10 mL), the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated by reduced pressure, and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 6:1) to provide 490 mg (70% yield) of the 2-pyrone product **12** as a colorless oil and 175 mg (25%) of the 4-pyrone product **13** as a colorless oil.



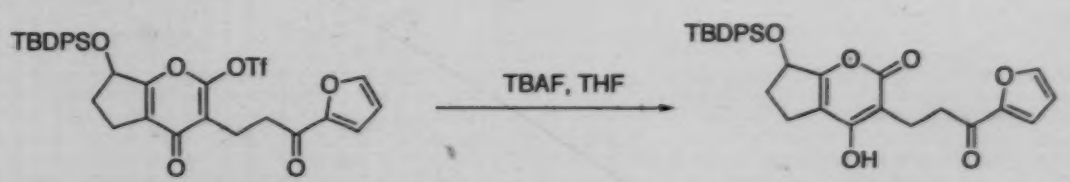
12

2-Pyrone Triflate, 12: R_f 0.42 (5:1 hexane/EtOAc); IR (thin film) 1732, 1680, 1649, 1584 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73-7.68 (m, 4H), 7.55 (dd, 1H, J = 0.5, 1.7 Hz), 7.42-7.36 (m, 6H), 7.19 (dd, 1H, J = 0.5, 3.5 Hz), 6.51 (dd, 1H, J = 1.7, 3.5 Hz), 5.02-4.99 (m, 1H), 3.18-3.12 (m, 2H), 2.89 (t, 2H, J = 7.3 Hz), 2.79-2.76 (m, 1H), 2.51-2.47 (m, 1H), 2.15-2.08 (m, 1H), 1.98-1.93 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.1, 163.3, 162.2, 154.4, 152.2, 146.4, 135.9, 135.8, 133.4, 132.7, 129.9 (2C), 127.75, 127.7, 118.2 (q, J_{CF} = 320.4 Hz, 1C), 118.8, 117.1, 112.8, 112.2, 74.2, 35.3, 31.8, 26.8, 24.1, 20.3, 19.2; HRMS (ESI) calcd for $C_{32}H_{31}O_8F_3NaSiS$ ($[M•Na]^+$) 683.1353, found 683.1357.



13

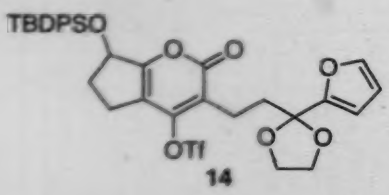
4-Pyrone Triflate, 13: R_f 0.63 (5:1 hexanes/EtOAc); IR (thin film) 1670, 1648, 1470 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.53 (dd, 1H, J = 0.7, 1.7 Hz), 7.42-7.35 (m, 6H), 7.20 (dd, 1H, J = 0.7, 3.6 Hz), 6.52 (dd, 1H, J = 1.7, 3.6 Hz), 5.18-5.16 (m, 1H), 3.13 (t, 2H, J = 7.2 Hz), 2.86 (t, 2H, J = 7.2 Hz), 2.72-2.66 (m, 1H), 2.38-2.32 (m, 1H), 2.06-1.97 (m, 1H), 1.89-1.82 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3, 178.1, 163.7, 154.3, 152.2, 146.3, 135.74, 135.68, 133.3, 132.5, 130.1, 130.0, 127.8, 127.7, 125.63, 118.2 (q, J_{CF} = 320.9 Hz, 1C), 117.2, 116.5, 112.2, 74.2, 35.5, 31.7, 26.7, 22.5, 19.1, 18.3; HRMS (ESI) calcd. for $C_{32}H_{32}O_8F_3SiS$ ($[M•H]^+$) 661.1533, found 661.1535.



13 **10**

To a solution of 4-pyrone triflate **13** (274.6 mg, 0.41 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.41 mL, 0.41 mmol). The reaction was complete upon addition of TBAF. Water (5 mL) was then added to

quench the reaction. The resulting solution was extracted with dichloromethane (10 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The organic solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Hexanes/EtOAc 3:1) to provide the 2-pyrone **10** as a colorless oil (201.6 mg, 93% yield).

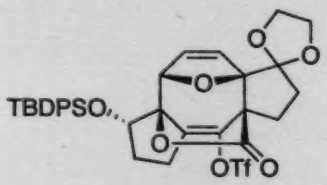


14

Preparation of 14. To a solution of 2-pyrone triflate **12** (1.24 g, 1.88 mmol) in benzene (15 mL) was added ethylene glycol (0.21 mL, 3.76 mmol) and TsOH (358 mg, 1.88 mmol). The mixture was refluxed using a Dean-Stark trap for 2 days. The reaction mixture was then quenched with water (20 mL) and extracted with dichloromethane (2 x 20 mL). The organic layer was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was concentrated by reduced pressure and the oily residue was purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford 1.06 g (80%) of ketal **14** as a colorless oil: R_f 0.45 (5:1 hexanes/EtOAc); IR (thin film) 1735, 1649, 1584, 1501 cm^{1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.69 (m, 4H), 7.42-7.39 (m, 6H), 7.33 (dd, 1H, J = 0.8, 1.7 Hz), 6.35 (dd, 1H, J = 0.8, 3.2 Hz), 6.28 (dd, 1H, J = 1.7, 3.2 Hz), 4.99 (t, 1H, J = 6.3 Hz), 4.02-3.96 (m, 4H), 2.79-2.72 (m, 1H), 2.67-2.62 (m, 2H), 2.53-2.49 (m, 1H), 2.29-2.24 (m, 2H), 2.18-2.12 (m, 1H), 1.94-1.90 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.3, 161.6, 154.0, 153.1, 142.6, 135.9, 135.8, 133.5, 132.6, 129.9, 129.9, 127.7, 127.6, 118.2 (q, J_{CF} = 320.4 Hz, 1C), 119.7, 112.5, 109.8, 107.4, 105.8, 74.2, 65.19, 65.16, 34.0, 31.7, 26.8, 24.2, 20.0, 19.2; HRMS (ESI) calcd. for $C_{34}H_{35}O_9F_3NaSiS$ ($[M•Na]^+$) 727.1615, found 727.1617.

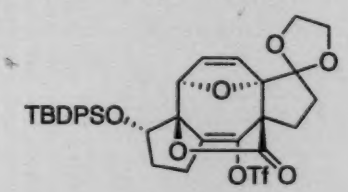
Irradiation of 14. A solution of **14** (217 mg, 0.31 mmol) in hexane (30 mL) was cooled in an ice-water bath. The solution was deoxygenated with nitrogen and irradiated under an atmosphere of nitrogen. After 30 min, the reaction was complete, as determined by TLC. The solvent was evaporated under reduced pressure and the

residue was purified by column chromatography (silica gel; hexanes/EtOAc 5:2) to afford two major isomers as colorless oils, 41.2 mg (19% yield) of the *exo* isomer and 123.7 mg (57% yield) of the *endo* isomer at a ratio of 1:3.



15c

Major *Endo* Cycloadduct, 15c: R_f 0.43 (5:2 Hexanes/EtOAc); IR (thin film) 1765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67-7.58 (m, 4H), 7.44-7.36 (m, 6H), 6.64 (dd, 1H, J = 1.8, 5.8 Hz), 6.21 (d, 1H, J = 5.8 Hz), 5.24 (d, 1H, J = 1.8 Hz), 4.47 (t, 1H, J = 5.3 Hz), 4.04-3.89 (m, 4H), 2.57-2.43 (m, 2H), 2.42-2.36 (m, 1H), 2.35-2.28 (m, 1H), 2.08-1.98 (m, 1H), 1.84-1.78 (m, 1H), 1.54-1.42 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 171.6, 143.0, 141.9, 135.8, 135.6, 134.9, 133.3, 132.5, 131.6, 130.3, 130.2, 128.0, 127.9, 118.1(q, J_{CF} = 320.4 Hz 1C), 112.8, 97.5, 89.9, 80.1, 77.5, 66.6, 65.8, 65.2, 33.8, 31.7, 27.0, 25.4, 22.4, 19.3; HRMS (ESI) calcd for $C_{34}H_{35}O_9F_3NaSiS$ ($[M•Na]^+$) 727.1615, found 727.1616.



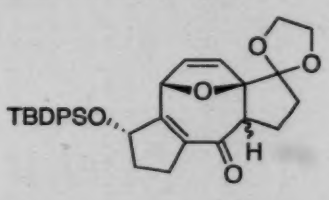
15d

Major *Exo* Cycloadduct, 15d: R_f 0.47 (5:2 hexanes/EtOAc); IR (thin film) 1765, 1708, 1589, 1472 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67-7.58 (m, 4H), 7.44-7.36 (m, 6H), 6.44-6.38 (m, 2H), 5.17 (d, 1H, J = 1.7 Hz), 4.37 (dd, 1H, J = 6.9, 11.2 Hz), 4.06-4.02 (m, 1H), 3.98-3.89 (m, 3H), 2.69-2.61 (m, 1H), 2.52-2.44 (m, 1H), 2.33-2.22 (m, 1H), 2.16-2.01 (m, 2H), 1.94-1.88 (m, 1H), 1.78-1,68 (m, 1H), 1.62-1.56 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 139.9, 135.74, 135.73, 135.5, 135.1, 133.2, 131.9, 130.2, 130.17, 127.9, 127.8, 118.3 (q, J_{CF} = 320.4 Hz 1C), 112.0, 93.0, 92.6, 79.2, 78.5, 65.8, 65.5, 64.8, 32.3, 30.7, 26.9, 22.7, 20.6, 19.2 (Note:

one carbon resonance could not be detected due to overlap.); HRMS (ESI) calcd for $C_{34}H_{35}O_9F_3NaSiS$ ([M•Na]$^+$) 727.1615, found 727.1614.

Reductive Deoxygenation of 15c. To a solution of **15c** (52.0 mg, 0.074 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (8.5 mg, 0.0074 mmol) followed by Bu_3SnH (30 μL, 0.11 mmol). The solution was refluxed for 1.5 h, before being quenched with water (10 mL) and extracted with CH_2Cl_2 (20 mL). The organic solvent was further washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the oily residue purified by column chromatography (silica gel; hexanes/EtOAc 7:1) to afford 4.1 mg (10%) of **21c**.

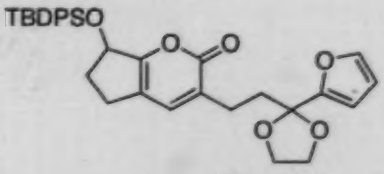
Reductive Deoxygenation of 15d. To a solution of **15d** (65.0 mg, 0.092 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (10.7 mg, 0.0092 mmol) followed by Bu_3SnH (37 μL, 0.14 mmol). The solution was refluxed for 1.5 h, before being quenched with water (10 mL) and extracted with CH_2Cl_2 (20 mL). The organic solvent was further washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the oily residue was purified by column chromatography (silica gel; hexanes/EtOAc 7:1) to afford 2.5 mg (5%) of **21d**.



17

Preparation of 17. To a solution of **15c** (65 mg, 0.092 mmol) in THF (5 mL) was added TBAF (0.10 mL, 0.10 mmol). The reaction was complete after 5 minutes. Water (10 mL) was then added. The resulting mixture was extracted by dichloromethane (20 mL). The organic phase was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was concentrated and the residue was purified by column chromatography to afford 40 mg (83%) of **17** as a colorless oil: R_f 0.45 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H), 7.48-7.38 (m, 6H), 6.51 (dd, 1H, J = 2.0, 6.0 Hz), 6.02 (dd, 1H, J = 1.5, 6.0 Hz), 5.38 (s, 1H), 5.10-5.05 (m, 1H), 4.02-3.92 (m, 4H), 3.12 (app t, 1H, J = 8.5 Hz), 2.44-2.38 (m, 1H), 2.26-2.18 (m, 1H), 2.14-2.00 (m, 3H), 1.88-1.68 (m, 2H), 1.58-1.50 (m, 1H), 1.12 (s,

9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 161.0, 138.1, 136.5, 135.9, 135.8, 133.8, 133.1, 130.0, 129.9, 127.9, 127.7, 127.3, 115.7, 94.4, 83.3, 80.5, 66.1, 64.9, 60.5, 33.1, 32.5, 29.8, 27.1, 23.8, 19.2.

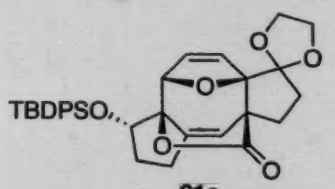


19

Preparation of 19. To a solution of **14** (800 mg, 1.14 mmol) in DMF (8 mL) was added $Pd(PPh_3)_4$ (65 mg, 0.057 mmol) and triethylsilane (0.36 mL, 2.28 mmol). The resulting mixture was heated at 60 °C for 20 mins. The solution became black once the reaction was complete. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was further washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 3:1) to afford 583.1 mg (92% yield) of product **19** as a colorless oil: R_f 0.45 (3:1 hexanes/EtOAc); IR (thin film) 1719, 1651, 1574 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.68 (m, 4H), 7.43-7.36 (m, 6H), 7.35 (dd, 1H, J = 0.8, 1.7 Hz), 6.99 (s, 1H), 6.36 (dd, 1H, J = 0.8, 3.2 Hz), 6.30 (dd, 1H, J = 1.7, 3.2 Hz), 4.97-4.95 (m, 1H), 4.02-3.95 (m, 4H), 2.64-2.56 (m, 3H), 2.34-2.28 (m, 3H), 2.12-2.05 (m, 1H), 1.92-1.86 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 159.5, 153.5, 142.4, 137.2, 136.0, 135.8, 134.1, 133.1, 129.8, 129.7, 128.0, 127.65, 127.6 (2C), 116.7, 109.9, 107.4, 106.2, 74.0, 65.2, 65.2, 35.2, 32.4, 26.9, 25.3, 19.2; HRMS (ESI) calcd for $C_{33}H_{36}O_6NaSi$ ($[M•Na]^+$) 579.2178, found 579.2173.

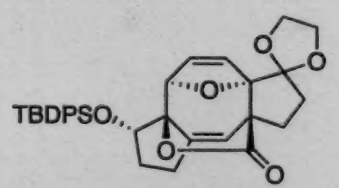
Irradiation of 19. A solution of **19** (226 mg, 0.41 mmol) in hexane (30 mL) was cooled with an ice-water bath. The solution was deoxygenated with nitrogen and irradiated under an atmosphere of nitrogen. After 3 h, the reaction was complete, as determined by TLC. The reaction mixture was concentrated and purified by column chromatography (silica gel; hexanes/EtOAc 8:1) to afford two major isomers as colorless oils, 84.7 mg (37% yield) of the *exo* isomer and 93.2 mg (41% yield) of the

endo isomer at a ratio of 1:1.1. Two minor isomers were also isolated as colorless oils: 25.6 mg (11% yield) of the *exo* isomer and a trace amount of the *endo* isomer.



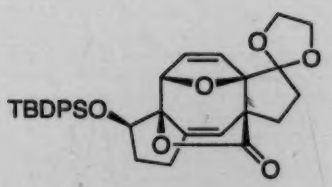
21c

Major *Endo* Cycloadduct, 21c: R_f 0.32 (3:1 hexanes/EtOAc); IR (thin film) 1750, 1588; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.62 (m, 4H), 7.44-7.34 (m, 6H), 6.57 (dd, 1H, J = 1.7, 5.9 Hz), 5.98 (d, 1H, J = 5.9 Hz), 5.45 (s, 1H), 5.23 (d, 1H, J = 1.7 Hz), 4.44 (t, 1H, J = 5.3 Hz), 4.04-3.98 (m, 2H), 3.96-3.92 (m, 2H), 2.66-2.62 (m, 1H), 2.43-2.38 (m, 1H), 2.38-2.30 (m, 1H), 2.19-2.14 (m, 1H), 1.98-1.92 (m, 1H), 1.59-1.46 (m, 3H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 153.6, 135.9, 135.7, 134.9, 133.8, 133.2, 132.1, 130.1, 129.9, 127.9, 127.7, 126.3, 113.4, 97.1, 92.8, 80.5, 77.7, 65.7, 65.0, 63.7, 34.3, 32.5, 27.4, 27.0, 26.8, 19.4; HRMS (ESI) calcd for $C_{33}H_{37}O_6Si$ ($[M•H]^+$) 557.2353, found 557.2350.



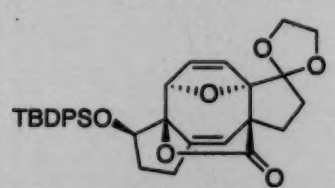
21d

Major *Exo* Cycloadduct, 21d: R_f 0.35 (3:1 hexanes/EtOAc); IR (thin film) 1749, 1471 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.42-7.36 (m, 6H), 6.49 (d, 1H, J = 5.8 Hz), 6.35 (dd, 1H, J = 2.0, 5.8 Hz), 5.54 (t, 1H, J = 2.4 Hz), 5.15 (d, 1H, J = 2.0 Hz), 4.36 (dd, 1H, J = 6.6, 10.9 Hz), 4.11-4.09 (m, 1H), 3.95-3.90 (m, 3H), 2.62-2.59 (m, 1H), 2.58-2.48 (m, 1H), 2.16-2.06 (m, 1H), 2.06-2.01 (m, 1H), 1.94-1.90 (m, 1H), 1.85-1.76 (m, 1H), 1.76-1.66 (m, 1H), 1.62-1.58 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 146.8, 136.0, 135.8 (2C), 134.3, 133.6, 132.4, 130.0 (2C), 127.8, 127.7, 124.9, 112.7, 95.3, 92.2, 78.9, 78.7, 65.4, 65.3, 62.9, 33.2, 31.9, 26.9, 26.6, 23.9, 19.2; HRMS (ESI) calcd for $C_{33}H_{36}O_6SiNa$ ($[M•Na]^+$) 579.2173, found 579.2179.



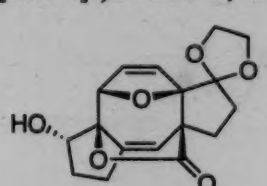
21a

Minor *Endo* Cycloadduct, 21a: R_f 0.31 (3:1 Hexanes: EtOAc); IR (film microscope) 1743, 1646, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78-7.70 (m, 4H), 7.46-7.38 (m, 6H), 6.17 (dd, 1H, J = 1.7, 5.9 Hz), 5.92 (d, 1H, J = 5.9 Hz), 5.46 (dd, 1H, J = 1.4, 2.6 Hz), 4.36 (d, 1H, J = 1.7 Hz), 4.02-3.94 (m, 2H), 3.94-3.83 (m, 2H), 3.73 (dd, 1H, J = 5.7, 8.9 Hz), 2.70-2.63 (m, 1H), 2.39-2.30 (m, 3H), 1.96-1.82 (m, 2H), 1.78-1.64 (m, 1H), 1.64-1.49 (m, 1H), 1.07 (s, 9H); HRMS (ESI) calcd for $C_{33}H_{36}O_6SiNa$ ($[M•Na]^+$) 579.2173, found 579.2171.



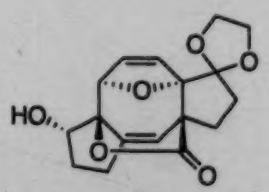
21b

Minor *Exo* Cycloadduct, 21b: R_f 0.32 (3:1 Hexanes: EtOAc); IR (film microscope) 1748, 1653, 1589, 1472 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.66 (m, 4H), 7.42-7.36 (m, 6H), 6.39 (d, 1H, J = 5.8 Hz), 5.78 (dd, 1H, J = 1.9, 5.8 Hz), 5.64 (t, 1H, J = 2.2 Hz), 4.07 (t, 1H, J = 3.4 Hz), 4.03-3.99 (m, 1H), 4.01 (d, 1H, J = 1.9 Hz), 3.93-3.84 (m, 3H), 2.72-2.60 (m, 2H), 2.52-2.46 (m, 1H), 2.04-1.98 (m, 1H), 1.98-2.82 (m, 3H), 1.78-1.70 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 148.8, 136.5, 136.4, 135.8, 134.2, 133.1, 132.8, 129.7, 129.6, 127.6, 127.5, 123.9, 112.6, 92.5, 91.8, 82.3, 75.6, 65.3, 65.28, 63.1, 33.2, 33.0, 26.9, 26.5, 25.1, 19.3; HRMS (ESI) calcd for $C_{33}H_{36}O_6SiNa$ ($[M•Na]^+$) 579.2173, found 579.2172.



30a

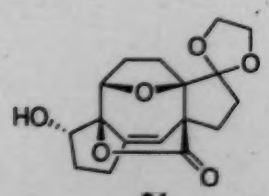
Preparation of 30a. To a solution of **21c** (165 mg, 0.30 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 0.33 mL, 0.33 mmol) dropwise. The resulting mixture was stirred at room temperature for 2 h. The reaction was then diluted with dichloromethane (10 mL) and water (10 mL). The mixture was extracted with dichloromethane (2x10 mL). The organic layers were combined, washed with brine (10 mL), and dried over $MgSO_4$. The solvent was concentrated and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 3:2) to afford 90.6 mg of alcohol (95% yield) as white solid: m.p. 169-171°C; R_f 0.24 (3:2 hexanes/EtOAc); IR (thin film) 3473, 1744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (dd, 1H, J = 1.8, 5.9 Hz), 5.94 (d, 1H, J = 5.9 Hz), 5.49 (t, 1H, J = 2.1 Hz), 5.04 (d, 1H, J = 1.8 Hz), 4.44 (t, 1H, J = 5.5 Hz), 4.04-3.98 (m, 2H), 3.96-3.89 (m, 2H), 2.67-2.61 (m, 1H), 2.50-2.32 (m, 2H), 2.31-2.24 (m, 1H), 1.98-1.92 (m, 2H), 1.78-1.74 (m, 1H), 1.58-1.54 (m, 1H) (alcohol proton not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 153.8, 135.1, 132.8, 126.5, 113.3, 97.2, 92.5, 79.9, 75.5, 65.6, 65.1, 63.5, 34.2, 32.6, 27.3, 26.8; HRMS (ESI) calcd for $C_{17}H_{18}O_6Na$ ($[M•Na]^+$) 341.0995, found 341.0995.



30b

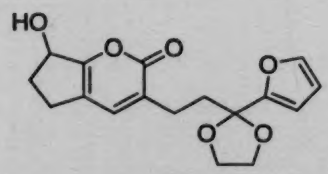
Preparation of 30b. To a solution of **21d** (120 mg, 0.22 mmol) in THF (5 mL) was added TBAF (1.0M in THF, 0.24 mL, 0.24 mmol) dropwise. The resulting mixture was stirred at room temperature for 2 h, before dilution with dichloromethane (20 mL) and water (10 mL) was added. The mixture was extracted with dichloromethane (2x10 mL). The organic layers were combined, washed with brine (10 mL), and dried over $MgSO_4$. The solvent was concentrated and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 3:2) to afford 68.5 mg of alcohol (98% yield) as a white solid: m.p. 170-171°C; R_f 0.26 (3:2 hexanes/EtOAc); IR (thin film) 3458, 1745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, 1H, J = 5.8 Hz), 6.31 (dd, 1H, J = 2.1, 5.8 Hz), 5.89 (t, 1H, J = 2.4 Hz), 4.95 (d, 1H, J = 2.1 Hz), 4.33 (dd,

1H, J = 6.9, 11.2 Hz), 4.08-4.02 (m, 1H), 3.93-3.88 (m, 3H), 2.89 (br s, 1H), 2.68-2.56 (m, 2H), 2.39-2.29 (m, 1H), 2.18-2.11 (m, 1H), 2.02-1.84 (m, 3H), 1.74-1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 147.4, 135.8, 134.2, 125.0, 112.6, 95.2, 92.2, 78.4, 77.0, 65.4, 65.3, 62.9, 33.2, 31.1, 26.5, 23.8; HRMS (ESI) calcd for $C_{17}H_{18}O_6Na$ ($[M•Na]^+$) 341.0995, found 341.0996. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.20; H, 5.71.



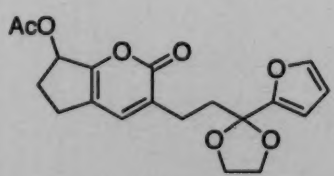
24

Preparation of 24. To a solution of **30a** (27 mg, 0.085 mmol) in EtOAc (2 mL) was added Pd/C (5 mg). The resulting mixture was stirred at room temperature under pressure from a hydrogen balloon for 1 h. The Pd/C was filtered out with celite, which was washed with EtOAc (20 mL). The solvent was concentrated under reduced pressure, and the residue purified by column chromatography (silica gel; hexanes/EtOAc 1:1) to afford 25.4 mg of product **24** (94% yield) as a white solid: m.p. 182-184°C; R_f 0.17 (1:1 hexanes/EtOAc); IR (thin film) 3492, 1743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (t, 1H, J = 2.1 Hz), 4.76-4.72 (m, 1H), 4.47 (dd, 1H, J = 5.4, 9.9 Hz), 4.06-4.01 (m, 1H), 3.98-3.84 (m, 3H), 2.86-2.79 (m, 1H), 2.59-2.52 (m, 2H), 2.42-2.38 (m, 1H), 2.14-2.09 (m, 2H), 2.02-1.86 (m, 3H), 1.85-1.75 (m, 3H), 1.58-1.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 174.7, 151.7, 128.5, 113.9, 93.5, 91.4, 76.3, 76.1, 65.5, 65.5, 59.5, 32.9, 32.6, 29.0, 27.3, 27.0 (Note: one carbon resonance could not be detected due to overlap.); HMRS (ESI) calcd for $C_{17}H_{20}O_6Na$ ($[M•Na]^+$) 343.1152, found 343.1153.



27

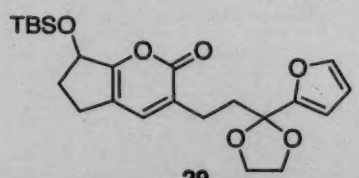
Preparation of 27. To a solution of **19** (165 mg, 0.30 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 0.33 mL, 0.33 mmol) dropwise. The resulting mixture was stirred at room temperature for 2h. The reation was then diluted with dichloromethane (10 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (2x10 mL), and the organic layers were combined, washed with brine (15 mL) and dried over $MgSO_4$. The solvent was removed and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 1:1) to afford 93.5 mg of alcohol **27** (98% yield) as a colorless oil: R_f 0.27 (1:1 hexanes/EtOAc); IR (thin film) 3418, 1714, 1645, 1573; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, 1H, J = 0.9, 1.8 Hz), 7.08 (s, 1H), 6.36 (dd, 1H, J = 0.9, 3.2 Hz), 6.31 (dd, 1H, J = 1.8, 3.2 Hz), 5.02-5.00 (m, 1H), 4.04-3.96 (m, 4H), 2.74-2.64 (m, 1H), 2.58-2.42 (m, 4H), 2.38 (br s, 1H), 2.34-2.30 (m, 2H), 1.98-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 159.3, 153.4, 142.5, 137.5, 128.2, 117.1, 109.9, 107.4, 106.1, 72.4, 65.2 (2C), 35.2, 31.1, 25.5, 25.3; HRMS (ESI) calcd for $C_{17}H_{19}O_6$ ($[M•H]^+$) 319.1176, found 319.1177.



28

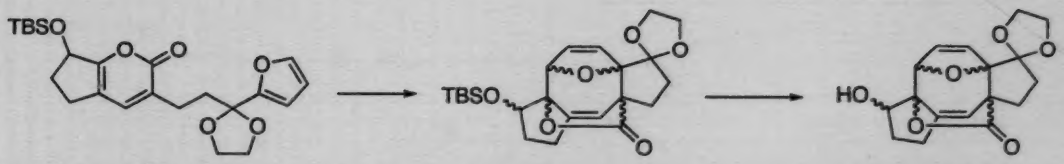
Preparation of 28. To a solution of **27** (22.7 mg, 0.063 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (17.6 μL, 0.126 mmol) and acetic anhydride (7.2 μL, 0.076 mmol). The resulting mixture was stirred at room temperature for 4 h. The reaction was then diluted with EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2x10 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure

and the residue purified by column chromatography (silica gel; hexanes/EtOAc 3:1) to provide 21.5 mg (95% yield) of **28** as a colorless oil: R_f 0.38 (3:1 hexanes/EtOAc); IR (thin film) 1720, 1655; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, 1H, J = 0.9, 1.8 Hz), 7.08 (s, 1H), 6.35 (dd, 1H, J = 0.9, 3.2 Hz), 6.31 (dd, 1H, J = 1.8, 3.2 Hz), 5.89-5.86 (m, 1H), 4.04-3.98 (m, 4H), 2.78-2.69 (m, 1H), 2.59-2.50 (m, 4H), 2.32-2.29 (m, 2H), 2.04 (s, 3H), 1.96-1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 170.3, 163.1, 155.4, 153.4, 142.5, 136.7, 129.3, 119.3, 109.9, 107.4, 106.1, 74.2, 65.2 (2C), 35.1, 29.4, 25.9, 25.3, 20.9; HRMS (ESI) calcd for $C_{19}H_{20}O_7Na$ ($[M•Na]^+$) 383.1101, found 383.1102.



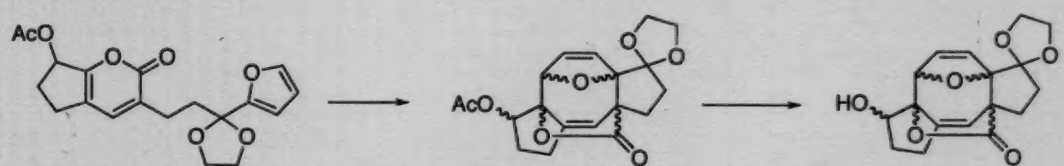
29

Preparation of 29. To a solution of **27** (27.2 mg, 0.063 mmol) in DMF (2 mL) was added imidazole (8.6 mg, 0.126 mmol) and TBSCl (14.2 mg, 0.094 mmol). The resulting mixture was stirred at room temperature for 4 h. The reaction was then diluted with EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2x10 mL) and the combined organic layers then washed with brine (15 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure, and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to provide 26.4 mg (97% yield) of **29** as a colorless oil: R_f 0.54 (5:1 hexanes/EtOAc); IR (thin film) 1717, 1652, 1575; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, 1H, J = 0.9, 1.8 Hz), 7.04 (s, 1H), 6.35 (dd, 1H, J = 0.9, 3.2 Hz), 6.30 (dd, 1H, J = 1.8, 3.2 Hz), 4.97-4.94 (m, 1H), 4.05-3.95 (m, 4H), 2.68-2.62 (m, 1H), 2.58-2.54 (m, 2H), 2.44-2.36 (m, 2H), 2.32-2.29 (m, 2H), 1.91-1.86 (m, 1H), 0.92 (s, 9H), 0.163 (s, 3H), 0.160 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 163.6, 159.7, 153.5, 142.5, 137.4, 127.9, 116.5, 109.8, 107.4, 106.2, 73.2, 65.2, 35.2, 32.5, 25.8, 25.4, 25.3, 18.3, -4.53, -4.83; HRMS (ESI) calcd for $C_{23}H_{33}O_6Si$ ($[M•H]^+$) 433.2040, found 433.2042.



29 30a-d

A solution of **29** (50.6 mg, 0.12 mmol) in hexane (20 mL) was cooled with an ice-water bath. The solution was deoxygenated with nitrogen and irradiated under an atmosphere of nitrogen. After 3 h the reaction was complete, as determined by TLC. The reaction mixture was concentrated and dissolved in THF (5 mL), followed by the addition of TBAF (1.0 M in THF, 0.18 mL, 0.18 mmol). The reaction was complete after 30 min. The solvent was then evaporated and the residue was filtered through a very short column (hexanes/EtOAc 1:1) to afford a mixture of four isomers (28.6 mg, 75% yield in two steps). The NMR indicated that the ratio of the four isomers was 10:9.4:1.0:2.4.

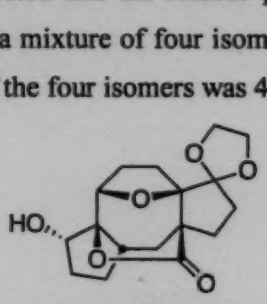


28 30a-d

A solution of **28** (43.2 mg, 0.12 mmol) in hexane (20 mL) was cooled with an ice-water bath. The solution was deoxygenated with nitrogen and irradiated under an atmosphere of nitrogen. After 3 h the reaction was complete as determined by TLC. The reaction mixture was concentrated and dissolved in methanol (5 mL), followed by the addition of potassium carbonate (50 mg, 0.36 mmol). After 1 h the reaction was complete and the reaction mixture was extracted with dichloromethane (10 mL), washed with brine (10 mL) and the combined organic layers dried with $MgSO_4$. The solvent was evaporated and the residue was passed through a short column (hexanes/EtOAc 1:1) to afford a mixture of four isomers (26.7 mg, 70% yield in two steps). The NMR indicated that the ratio of the four isomers was 3.1:3.8:1.0:1.9.

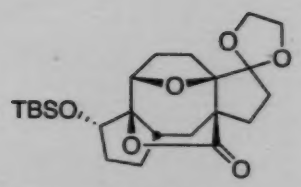
27 30a-d

A solution of **27** (38.2 mg, 0.12 mmol) in hexane (20 mL) was cooled with an ice-water bath. The solution was deoxygenated with nitrogen and irradiated under an atmosphere of nitrogen. After 2.5 h the reaction was complete, as determined by TLC. The solvent was evaporated and the residue passed through a short column (hexanes/EtOAc 1:1) to afford a mixture of four isomers (32.0 mg, 84% yield). The NMR indicated that the ratio of the four isomers was 4.0:3.5:1.0:2.0.



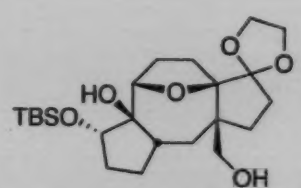
31

Preparation of 31. To a solution of **30a** (450 mg, 1.40 mmol) in EtOAc (10 mL) was added 5 wt. % Pd/C (40 mg). The resulting mixture was stirred at room temperature with a hydrogen balloon for 5 h. The Pd/C was filtered out with a short plug of celite, which was washed with EtOAc (20 mL). The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 1:1) to afford 417 mg of single product **31** (92% yield) as a white solid: R_f (0.53 hexanes/EtOAc 1:1); IR (cast film) 3457, 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.61 (d, 1H, J = 6.0 Hz), 4.25 (dd, 1H, J = 1.5, 6.0 Hz), 4.14-4.10 (m, 1H), 4.02-3.92 (m, 3H), 2.78-2.64 (m, 2H), 2.40-2.31 (m, 1H), 2.24-1.96 (m, 6H), 1.96-1.90 (m, 1H), 1.78-1.70 (m, 1H), 1.56-1.52 (m, 1H), 1.44-1.38 (m, 2H), 1.24-1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 114.6, 91.8, 91.0, 79.4, 77.8, 65.55, 65.50, 56.7, 36.4, 34.7, 33.9, 32.5, 31.5, 28.4, 28.1, 25.1; HRMS (ESI) calcd for $C_{17}H_{23}O_6$ ($[M•H]^+$) 323.1489, found 323.1487.



32

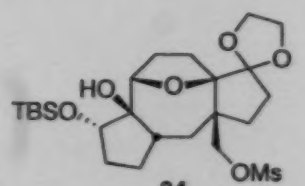
Preparation of 32. To a solution of **31** (185 mg, 0.57 mmol) in DMF (5 mL) was added imidazole (77.6 mg, 1.14 mmol) and TBSCl (129 mg, 0.85 mmol). The resulting solution was stirred at room temperature for 2 h before diethyl ether (20 mL) was added. The organic layer was washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. The solvent was concentrated and the residue purified by column chromatography (silica gel; hexanes/EtOAc 6:1) to afford 236 mg (95%) of **32** as a colorless oil: R_f (0.47 hexanes/EtOAc 6:1); IR (thin film) 1754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (d, 1H, J = 6.0 Hz), 4.18 (dd, 1H, J = 2.4, 5.6 Hz), 4.14-4.10 (m, 1H), 4.01-3.92 (m, 3H), 2.74-2.62 (m, 2H), 2.24-1.90 (m, 8H), 1.80-1.72 (m, 1H), 1.50-1.24 (m, 4H), 0.84 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 114.69, 92.2, 91.0, 79.9, 78.2, 65.5, 65.4, 56.8, 36.7, 34.5, 34.0, 32.6, 31.7, 28.6, 28.1, 25.7, 25.1, 17.8, -4.5, -5.0.



33

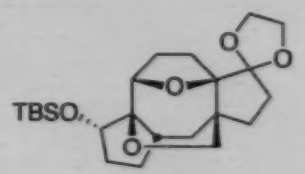
Preparation of 33. To a solution of **32** (126 mg, 0.29 mmol) in diethyl ether (10 mL) was added lithium aluminum hydride (11 mg, 0.29 mmol) at 0°C. The resulting mixture was stirred for 1 h. Water (5 mL) was then added to quench the reaction. The aqueous phase was extracted with diethyl ether (20 mL), and the combined organic layers washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 2:1) to afford 117 mg of **33** as a colorless oil (92%): R_f 0.24 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (br s, 1H), 4.32 (d, 1H, J = 10.3 Hz), 4.21 (d, 1H, J = 6.9 Hz), 4.18-4.14 (m, 1H), 4.02 (dd, 1H, J = 3.6,

7.1 Hz), 3.98-3.88 (m, 3H), 3.30-3.24 (m, 2H), 2.39-2.28 (m, 3H), 2.25-2.18 (m, 1H), 1.96-1.68 (m, 6H), 1.56 (dd, 1H, J = 1.8, 5.2 Hz), 1.48-1.24 (m, 4H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.8, 95.1, 84.267, 84.261, 82.0, 75.3, 66.0, 65.2, 49.2, 41.0, 37.5, 34.7, 32.7, 31.0, 30.8, 30.7, 28.3, 25.9, 18.0, -4.6, -4.8; HRMS (ESI) calcd for $C_{23}H_{40}O_6SiNa$ ($[M•Na]^+$) 463.2486, found 463.2486.



34

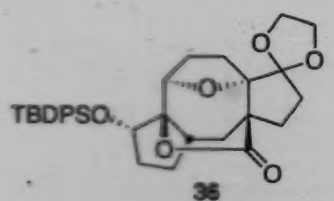
Preparation of 34. To a solution of **33** (30 mg, 0.068 mmol) in dichloromethane (2 mL) was added triethylamine (11 μL, 0.082 mmol) and methanesulfonyl chloride (6.3 μL, 0.082 mmol). The solution was stirred for 2 h before aqueous ammonium chloride (2 mL) was added. The reaction was extracted with dichloromethane (10 mL) and the combined organic layers washed with brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 3:1) to afford 32 mg of **34** as a colorless oil (90%): R_f 0.53 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (d, 1H, J = 10.5 Hz), 4.23 (d, 1H, J = 7.0 Hz), 4.20 (d, 1H, J = 10.5 Hz), 4.18-4.14 (m, 1H), 4.02 (dd, 1H, J = 3.5, 6.9 Hz), 3.98-3.88 (m, 3H), 3.01 (s, 3H), 3.28 (br s, 1H), 2.43-2.27 (m, 3H), 2.25-2.14 (m, 1H), 1.98-1.54 (m, 8H), 1.38-1.22 (m, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).



35

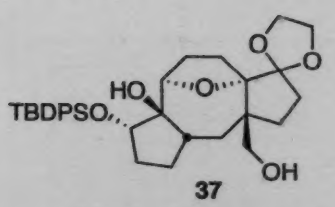
Preparation of 35. To a solution of **33** (55 mg, 0.13 mmol) in THF (5 mL) was added triphenylphosphine (52 mg, 0.20 mmol), iodine (51 mg, 0.20 mmol) and imidazole (18 mg, 0.26 mmol). The resulting solution was stirred at room

temperature for 6 h before water (10 mL) was added. The reaction was extracted with dichloromethane (10 mL) and the combined organic layers washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 4:1) to give 43 mg (82%) of **35** as a colorless oil: R_f 0.32 (4:1 hexanes/EtOAc); IR (thin film) 2951, 2893, 1471 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 (dd, 1H, J = 3.5, 8.2 Hz), 4.39 (d, 1H, J = 7.0 Hz), 4.28-4.24 (m, 1H), 4.08-4.03 (m, 1H), 3.96-3.90 (m, 2H), 3.82 (dd, 1H, J = 2.0, 6.3 Hz), 3.35 (d, 1H, J = 8.0 Hz), 2.58-2.50 (m, 1H), 2.22-2.02 (m, 5H), 1.96-1.84 (m, 1H), 1.72-1.60 (m, 3H), 1.50-1.40 (m, 3H), 1.22-1.12 (m, 2H), 0.82 (s, 9H), 0.013(s, 3H), 0.004 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.1, 93.0, 85.7, 81.9, 80.6, 74.5, 65.4, 65.2, 45.2, 37.4, 36.8, 34.2, 32.8, 32.2, 30.5, 29.9, 27.5, 25.8, 17.8, -4.4, -5.0; HRMS (ESI) calcd for $C_{23}H_{38}O_5SiNa$ ($[M•Na]^+$) 445.2381, found 445.2380.



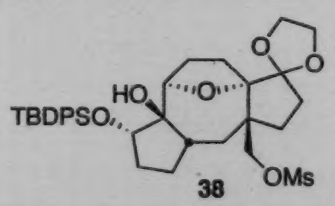
36

Preparation of 36. To a solution of **21d** (50 mg, 0.09085 mmol) in EtOAc (2 mL) was added PtO_2 (5 mg). The resulting mixture was stirred at room temperature under pressure from a hydrogen balloon for 1 h. The solid residue was filtered out with celite, which was washed with EtOAc (20 mL). The solvent was concentrated under reduced pressure, and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford 45 mg of product **36** (90% yield) as a colorless oil: R_f 0.17 (1:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.60 (m, 4H), 7.44-7.34 (m, 6H), 4.98 (d, 1H, J = 7.1 Hz), 4.22-4.10 (m, 2H), 4.05-3.90 (m, 3H), 2.82 (dd, 1H, J = 8.3, 13.0 Hz), 2.66 (ddd, 1H, J = 2.1, 9.3, 13.7 Hz), 2.48 (ddd, 1H, J = 3.6, 9.7, 12.9 Hz), 2.30 (dt, 1H, J = 3.4, 12.8 Hz), 2.16-1.80 (m, 1H), 2.02-1.90 (m, 1H), 1.86-1.66 (m, 5H), 1.64-1.38 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 177.1, 135.9, 134.1, 132.8, 129.8, 127.7, 127.6, 114.6, 91.4, 91.2, 79.5, 78.2, 65.3, 65.1, 55.2, 41.2, 32.5, 31.9, 31.5, 31.3, 28.3, 27.7, 26.9, 24.1, 19.1.



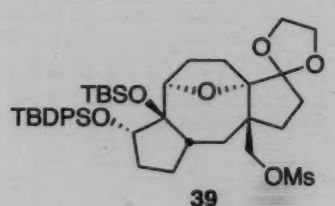
37

Preparation of 37. Lactone **36** was treated with lithium aluminium chloride following the procedure given above for **32**. Purification by column chromatography (silica gel; hexanes/EtOAc 5:1) afforded diol **37** (63 mg, 89%) as a colorless oil: R_f 0.24 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.70 (m, 4H), 7.42-7.38 (m, 6H), 4,69 (t, 1H, J = 5.8 Hz), 4.14-3.93 (m, 5H), 3.82 (d, 1H, J = 10.7 Hz), 3.45 (d, 1H, J = 10.7 Hz), 2.77 (br s, 1H), 2.62 (t, 1H, J = 12.3 Hz), 2.12-2.02 (m, 2H), 2.02-1.88 (m, 4H), 1.84-1.72 (m, 2H), 1.64-1.50 (m, 4H), 1.42-1.26 (m, 2H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 136.3, 136.2, 134.8, 133.9, 129.5, 129.4, 127.5, 127.4, 117.0, 92.2, 84.1, 83.9, 81.9, 66.9, 65.9, 64.5, 50.4, 42.7, 40.0, 33.2, 32.1, 31.0, 30.7, 27.3, 27.0, 25.4, 19.3.



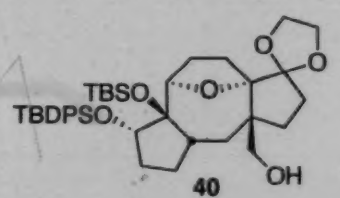
38

Preparation of 38. Diol **37** was treated with methanesulfonyl chloride following the procedure given above for **33**. Purification by column chromatography (silica gel; hexanes/EtOAc 6:1) afforded **38** (75 mg, 95%) as a colorless oil: R_f 0.52 (6:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.70 (m, 4H), 7.42-7.36 (m, 6H), 4.70 (dd, 1H, J = 4.6, 7.4 Hz), 4.34 (d, 1H, J = 9.0 Hz), 4.18 (d, 1H, J = 9.0 Hz), 4.06-3.80 (m, 5H), 3.01 (s, 3H), 2.56 (t, 1H, J = 12.2 Hz), 2.10-1.90 (m, 5H), 1.84-1.72 (m, 3H), 1.72-1.58 (m, 3H), 1.58-1.52 (m, 1H), 1.49-1.38 (m, 3H), 1.12 (s, 9H).



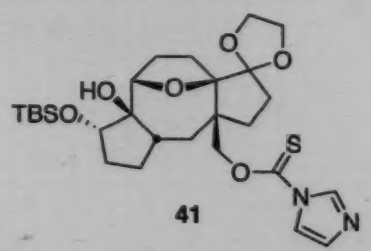
39

Preparation of 39. To a solution of **38** (30 mg, 0.047 mmol) in CH_2Cl_2 (2 mL) was added tert-butyldimethylsilyl trifluoromethanesulfonate (55 μL, 0.24 mmol) and triethyl amine (66 μL, 0.47 mmol). The solution was stirred for 6 h and purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford 32 mg of product **39** (92% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.68 (m, 4H), 7.42-7.30 (m, 6H), 4.71 (dd, 1H, J = 4.6, 7.4 Hz), 4.34 (d, 1H, J = 8.9 Hz), 4.18 (d, 1H, J = 8.9 Hz), 4.10-3.90 (m, 5H), 3.01 (s, 3H), 2.60-2.50 (m, 1H), 2.20-1.59 (m, 10H), 1.42-1.22 (m, 4H), 1.12 (s, 9H), 0.78 (s, 9H), -0.18 (s, 3H), -0.38 (s, 3H).



40

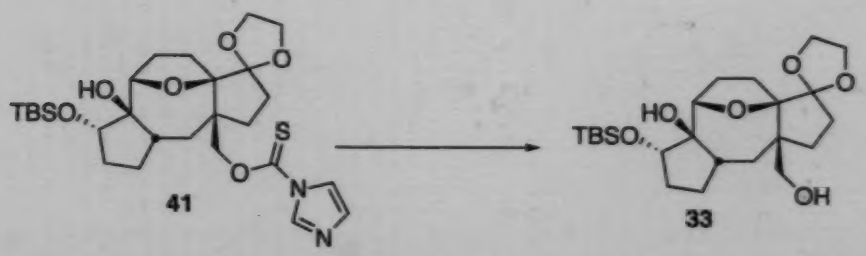
Preparation of 40. To a solution of **39** (32 mg, 0.042 mmol) in diethyl ether (5 mL) was added lithium aluminum hydride (5.0 mg, 0.13 mmol). The resulting mixture was stirred at reflux for 2 h. Water (5 mL) was then added to quench the reaction. The aqueous phase was extracted with diethyl ether (20 mL), and the combined organic layers washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 3:1) to afford 20 mg of **40** as a colorless oil (72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.70 (m, 4H), 7.42-7.36 (m, 6H), 4.70 (dd, 1H, J = 4.2, 8.4 Hz), 4.16-3.96 (m, 5H), 3.85 (d, 1H, J = 10.6 Hz), 3.46 (d, 1H, J = 10.6 Hz), 2.72 (br s, 1H), 2.62 (t, 1H, J = 13.4 Hz), 2.20-1.60 (m, 10H), 1.38-1.20 (m, 4H), 1.10 (s, 9H), 0.72 (s, 9H), -0.18 (s, 3H), -0.38 (s, 3H).



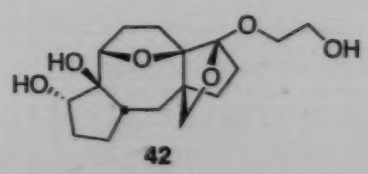
41

Preparation of 41. To a solution of **33** (25 mg, 0.057 mmol) was added thiocarbonyldiimidazole (20 mg, 0.12 mmol) and DMAP (28 mg, 0.23 mmol) in THF

(2 mL). After 5 h, the reaction was diluted with diethyl ether (10 mL), washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure and the residue was purified by column chromatography (silica gel; hexane/EtOAc 6:1) to give 25 mg of **41** (80% yield): R_f 0.35 (6:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.67 (s, 1H), 7.02 (s, 1H), 5.40 (d, 1H, J = 10.0 Hz), 5.02 (d, 1H, J = 10.0 Hz), 4.38 (d, 1H, J = 6.4 Hz), 4.20-3.84 (m, 5H), 2.60-2.40 (m, 3H), 2.40-2.26 (m, 1H), 2.04-1.76 (m, 8H), 1.60-1.36 (m, 4H), 0.82 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

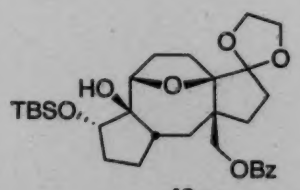


To a solution of **41** (25 mg, 0.045 mmol) in benzene (2 mL) was added tributyltin hydride (36 μL, 0.14 mmol) and a crystal of AIBN (ca. 5 mg). The solution was stirred at reflux for 30 min and purified by column chromatography (silica gel; hexanes/EtOAc 3:1). Compound **33** (7.0 mg, 35% yield) was the only product that could be recovered.



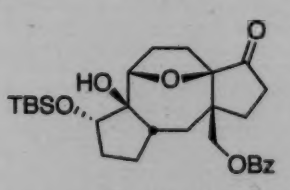
Preparation of 42. Diol **33** was treated with lithium aluminium chloride following the procedure given above for **43**. Purification by column chromatography (silica gel; hexanes/EtOAc 1:1) afforded **42** (31 mg, 87%) as a colorless oil: R_f 0.22 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, 1H, J = 8.0 Hz), 4.16 (dd, 1H, J = 3.5, 6.5 Hz), 4.04 (dd, 1H, J = 3.0, 7.5 Hz), 3.97 (ddd, 1H, J = 3.0, 6.0, 12.0 Hz), 3.88 (ddd, 1H, J = 2.5, 6.5, 11.5 Hz), 3.82 (d, 1H, J = 8.0 Hz), 3.74 (ddd, 1H, J =

2.5, 6.5, 12.5 Hz), 3.68 (ddd, 1H, J = 2.5, 6.0, 12.5 Hz), 2.70 (br s, 1H), 2.42-2.12 (m, 4H), 2.06-1.90 (m, 2H), 1.82-1.22 (m, 10H).



43

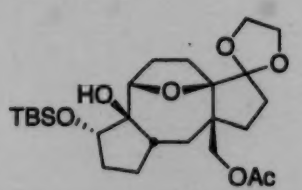
Preparation of 43. To a solution of **33** (65 mg, 0.15 mmol) in dichloromethane (5 mL) was added triethylamine (25 μL, 0.18 mmol) and benzoyl chloride (23 μL, 0.18 mmol). The solution was stirred for 2.5 h before aqueous ammonium chloride (2 mL) was added. The reaction was extracted with dichloromethane (10 mL) and the combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 3:1) to afford 71 mg of **43** as a colorless oil (87%): R_f 0.43 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.02 (m, 2H), 7.56-7.52 (m, 1H), 7.42-7.40 (m, 2H), 5.01 (d, 1H, J = 11.5 Hz), 4.62 (dd, 1H, J = 1.6, 11.5 Hz), 4.23 (d, 1H, J = 7.0 Hz), 4.18-4.16 (m, 1H), 4.02 (dd, 1H, J = 3.1, 6.8 Hz), 3.98-3.86 (m, 3H), 2.90 (s, 1H), 2.54-2.50 (m, 1H), 2.42-2.38 (m, 2H), 2.22-2.18 (m, 1H), 2.04-1.64 (m, 8H), 1.42-1.28 (m, 3H), 0.88 (s, 9H), 0.027 (s, 3H), 0.023 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 132.7, 130.7, 129.6, 128.3, 114.9, 94.6, 84.8, 83.2, 82.4, 69.7, 65.6, 64.8, 50.5, 40.6, 34.1, 33.6, 32.8, 31.1, 30.4, 29.9, 28.4, 25.9, 17.9, -4.6, -4.8.



44

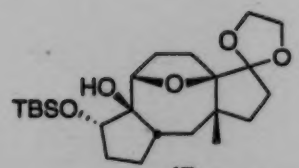
Preparation of 44. To a solution of **43** (20 mg, 0.037 mmol) in 2 mL acetone/water (1:1) was added *p*-toluenesulfonic acid monohydrate (5 mg, 0.026 mmol). The solution was refluxed for 5 h, then diethyl ether (5 mL) and brine (5 mL) were added. The organic phase was dried over $MgSO_4$. The solvent was removed under reduce

pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 3:1) to afford 17 mg of **44** as a colorless oil (90%): R_f 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H), 7.58-7.52 (m, 1H), 7.44-7.40 (m, 2H), 4.57 (d, 1H, *J* = 11.7 Hz), 4.46 (d, 1H, J = 7.3 Hz), 4.39 (d, 1H, *J* = 11.7 Hz), 4.04 (dd, 1H, *J* = 3.5, 6.9 Hz), 2.50-2.16 (m, 8H), 2.14-2.04 (m, 1H), 1.92-1.78 (m, 4H), 1.70-1.74 (m, 1H), 1.52-1.44 (m, 1H), 1.40-1.34 (m, 1H), 0.82 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 213.6, 166.5, 133.1, 129.8, 129.7, 128.4, 91.3, 84.8, 83.0, 77.3, 69.4, 48.2, 40.2, 34.1, 33.2, 31.9, 31.4, 31.0, 30.0, 27.9, 25.8, 17.9, -4.7, -4.8.



46

Preparation of 46. To a solution of **33** (35 mg, 0.079 mmol) in dichloromethane (5 mL) was added triethylamine (13 μL, 0.095 mmol) and acetyl chloride (6.8 μL, 0.095 mmol). The solution was stirred for 0.5 h before aqueous ammonium chloride (2 mL) was added. The reaction was extracted with dichloromethane (10 mL) and the combined organic layers washed with brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 3:1) to afford 35 mg of **46** as a colorless oil (92%): R_f 0.45 (3:1 hexanes/EtOAc); IR (microscope) 3473, 1708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (dd, 1H, *J* = 4.5, 7.1 Hz), 4.22 (d, 1H, *J* = 10.5 Hz), 4.02-3.84 (m, 6H), 2.42 (t, 1H, *J* = 3.1 Hz), 2.22-2.10 (m, 1H), 2.10-1.98 (m, 3H), 2.04 (s, 3H), 1.98-1.86 (m, 2H), 1.78-1.70 (m, 2H), 1.70-1.56 (m, 3H), 1.48-1.40 (m, 1H), 1.30-1.20 (m, 2H), 1.02 (br s, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 171.4, 116.9, 91.9, 83.5, 82.8, 82.1, 67.4, 65.7, 64.4, 47.9, 42.6, 37.5, 33.9, 33.4, 31.3, 30.4, 27.2, 25.8, 24.8, 21.0, 17.9, -4.4, -4.9; HRMS (ESI) calcd. for $C_{25}H_{42}O_7SiNa$ ($[M•Na]^+$) 505.2592, found 505.2593.



47

Preparation of 47. A solution of acetate **46** (35 mg, 0.073 mmol) in 2.0 mL of 95: 5 HMPA-H_2O in a quartz tube was irradiated for 8 h with a 450-W Hanovia Hg lamp. The crude photolysate solution was poured into 10 mL of Et_2O and washed with water (10 mL) and brine (5 mL). The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 6:1) to afford 14 mg of **47** as a colorless oil (45%) and 11 mg of starting **46** (30%): R_f 0.45 (6:1 hexanes/EtOAc); IR (microscope) 3509 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.52 (app t, 1H, J = 5.1 Hz), 4.02-3.84 (m, 5H), 2.50 (t, 1H, J = 3.0 Hz), 2.20-2.10 (m, 1H), 2.10-2.00 (m, 3H), 1.98-1.82 (m, 3H), 1.70-1.60 (m. 3H), 1.58-1.56 (m, 1H), 1.46-1.38 (m, 3H), 1.05 (s, 3H), 0.96 (br s, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 117.3, 92.8, 83.8, 82.9, 81.7, 65.5, 64.4, 44.8, 44.2, 43.2, 38.8, 33.4, 31.3, 30.8, 27.2, 25.8, 25.4, 24.7,17.9, -4.4, -4.9; HRMS (ESI) calcd. for $C_{23}H_{40}O_5SiNa$ ($[M•Na]^+$) 447.2537, found 447.2536.

2.5 References and Notes

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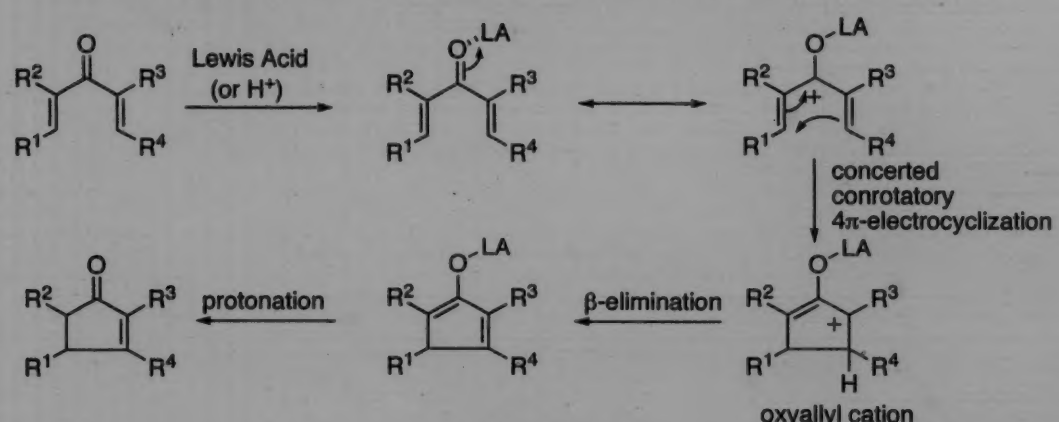
CHAPTER 3

INTERMOLECULAR TRAPPING OF THE NAZAROV INTERMEDIATE: DOMINO ELECTROCYCLIZATION/SCHMIDT-TYPE REARRANGEMENT WITH ALKYL AZIDE

3.1 Introduction

In 1942, Nazarov published the first example of the Nazarov cyclization.[1] This reaction allows the synthesis of cyclopentenones from cross-conjugated divinyl ketones. The Nazarov cyclization is catalyzed by a strong Brønsted or Lewis acid, and in most cases more than one equivalent of the acid is required. The usefullness of this reaction is demonstrated by the creation of two new stereocenters and one carbon-carbon bond in a single operation.[2] This reaction has been proven to be useful and efficient in the synthesis of cyclopentenoid and polyquinane natural products.[3-12] The reaction mechanism first involves coordination of the Lewis acid to the carbonyl group of the divinyl ketone (Scheme 1). This results in a pentadienyl cation, which undergoes a concerted conrotatory 4π electrocyclic ring closure[13] to yield the key oxyallyl cationic intermediate. β-Elimination of a proton next to the stable carbocation then occurs to form a double bond having the highest degree of substitution. Protonation of the Lewis-acid bound enolate reinstalls the ketone.



Scheme 1

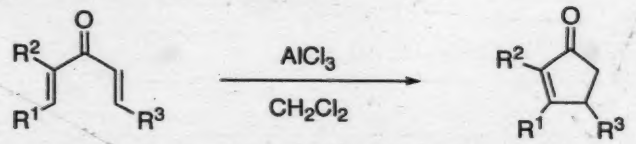
Usually, proton elimination occurs to generate the most highly substituted double bond; however, the other regioisomer cannot be completely avoided. To obtain better regioselectivity, electron-donating and withdrawing groups can be used to polarize the cross-conjugated dienones in the Nazarov reaction (Scheme 2).[14] Another approach to control the regioselectivity uses silicon to stabilize a β-carbocation, which is called the β-effect (Scheme 2).[15] TMS behaves like a proton and is eliminated after cyclization. This silicon-directed approach can be used to regioselectively form the double bond on the less substituted side of the product.

Diastereoselectivity in the Nazarov cyclization is often low since the substituents α to the ketone are easily epimerized in the presence of strong Lewis or Brønsted acids. The ratio of product isomers will be established after equilibration due to proton transfer. West and co-worker found that high diastereoseletivity could be obtained by using bridged bicyclic dienones.[16] The Nazarov cyclization is an example of a Lewis acid catalyzed reaction, therefore it is potentially possible to use a chiral Lewis acid to control the direction of the conrotatory ring closure. The existing drawbacks associated with an asymmetric Nazarov reaction are lower enantioselectivity and the need for stoichiometric amounts of chiral Lewis acid. There are only a few asymmetric examples reported so far (Scheme 3).[17,18] Copper-pybox or scandium-pybox complexes have been used as chiral Lewis acids to achieve moderate to good enantioselectivities in these two examples.

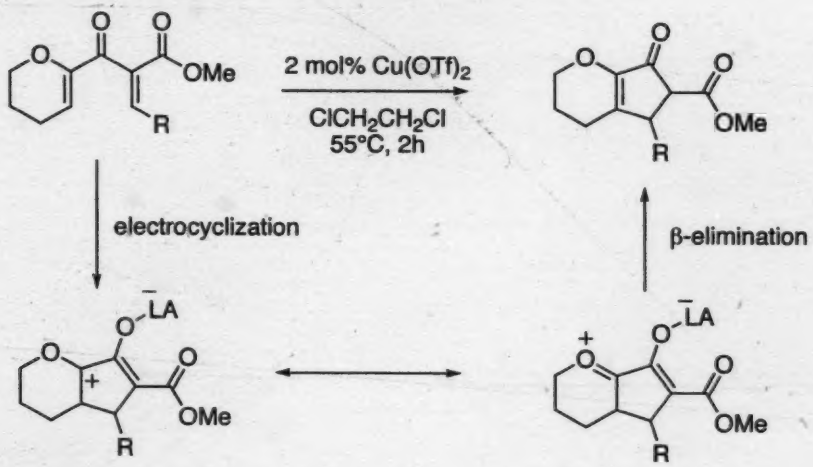
In summary, the Nazarov cyclization is a powerful methodology to efficiently build a cyclopentenone skeleton. There are still, however, some issues that need to be considered and resolved, such as (1) the use of multiple equivalents of strong Lewis acid; (2) regioselective elimination; (3) stereoselective protonation of the enolate; and (4) the loss of a stereocenter during the elimination of proton. Progress in the areas of regioselectivity and stereoselectivity has been mentioned above. Preservation of the stereocenter generated in the cyclization step remains a challenge.

Regioselectivity:

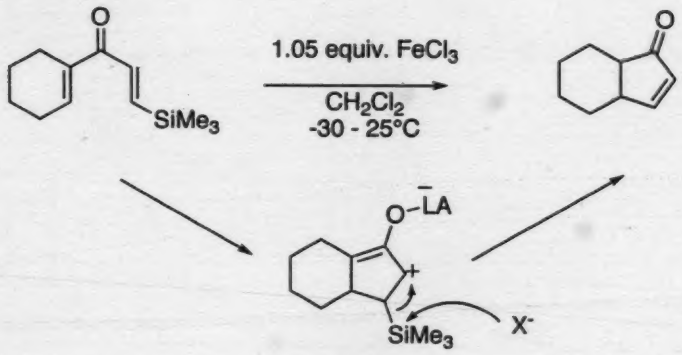
a: most electron-rich double bond dominates



b: effect of electron-donating and withdrawing substituents



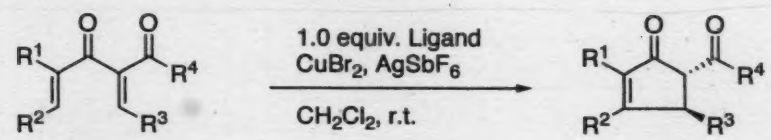
c: silicon-directed



Scheme 2

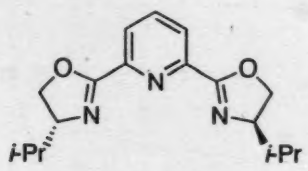
Stereoselectivity using chiral Lewis acids:

a:

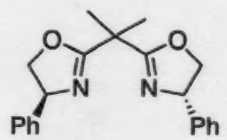


R^4 = OEt, Cu-pybox

R^4 = NEt_2, Cu-box

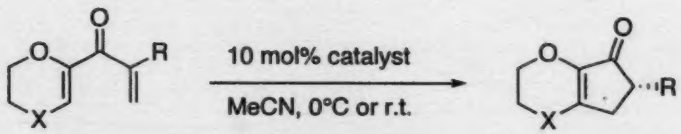


pybox



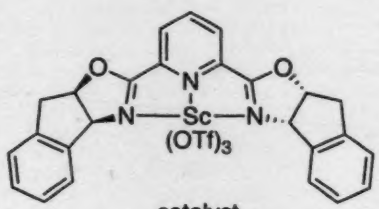
box

b:



X = CH_2, O

72-97 % ee



catalyst

Scheme 3

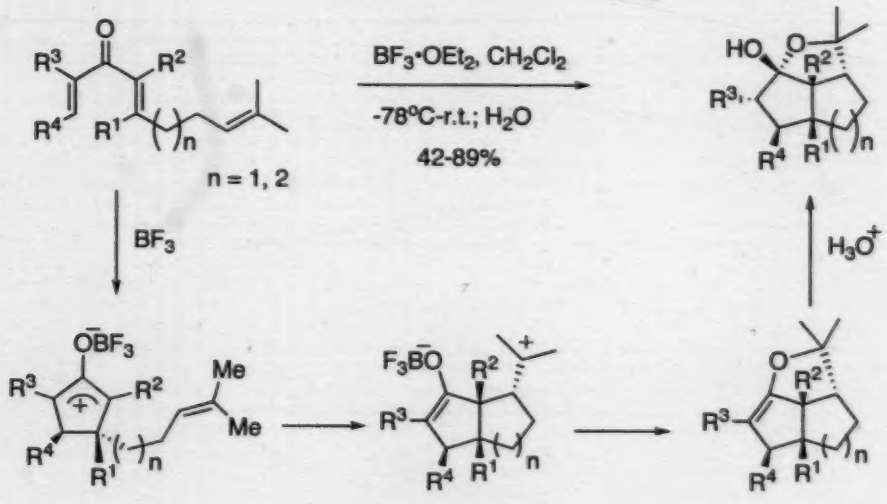
Recently, development of the Nazarov cyclization has been of great interest in the synthetic community especially in the area of the asymmetric Nazarov reaction, interception of cationic intermediates,[19-27] the use of highly reactive allene substrates[28-30] and even the reverse Nazarov reaction.[31,32] In the classic Nazarov cyclization, β-elimination of a proton occurs after the generation of an oxyallyl cationic intermediate, resulting in the formation of one carbon-carbon bond and two stereocenters. The "Interrupted Nazarov", named by West, involves capture of the oxyallyl cation by other nucleophiles before proton elimination takes place. This

process allows for the generation of multiple stereocenters and carbon-carbon bonds, resulting in more complicated polycyclic ring systems than the classic Nazarov cyclization. The interrupted Nazarov reaction also successfully preserves the initially formed stereocenter, which is destroyed in the classic Nazarov cyclization.

Herein, a general overview of the interception of cationic intermediates in the Nazarov reaction will be presented.

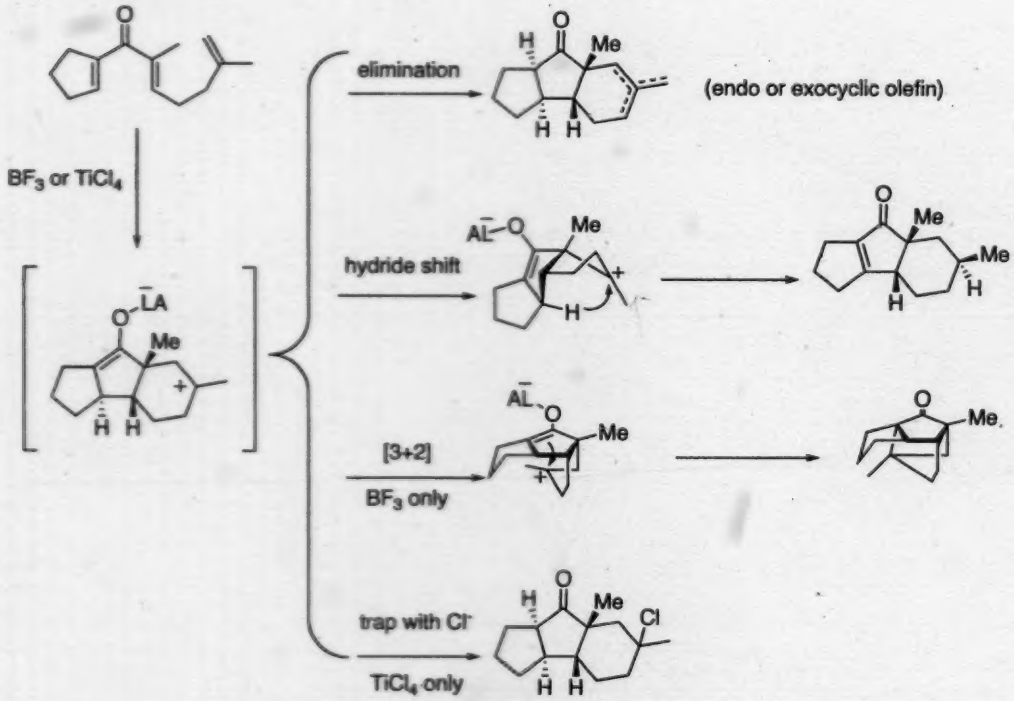
3.1.1 Intramolecular Trapping of the Nazarov Intermediate with Alkenes

West and co-workers described the first examples of the interrupted Nazarov reaction in 1998.[20] In this domino process, simple acyclic, achiral trienones were converted to diquinanes in the presence of $BF_3{\cdot}OEt_2$ (Scheme 4). The substrates first underwent conrotatory 4π-electrocyclization, followed by cation-olefin cyclization, capture of the 3° cation by an enolate oxygen, and finally stereoselective protonation of the enol ether during work-up to provide the functionalized polycyclic product as a single isomer. Four to five stereocenters and two new carbon-carbon bonds were successfully formed in a single operation. When n = 2, 6-*exo* cyclization proceeded in an analogous manner to provide a mixture of two diastereoisomers (5:1) in a decreased yield. Trapping with a tethered alkene has only been observed for substrates with substitution at both α-positions of the dienone.



Scheme 4

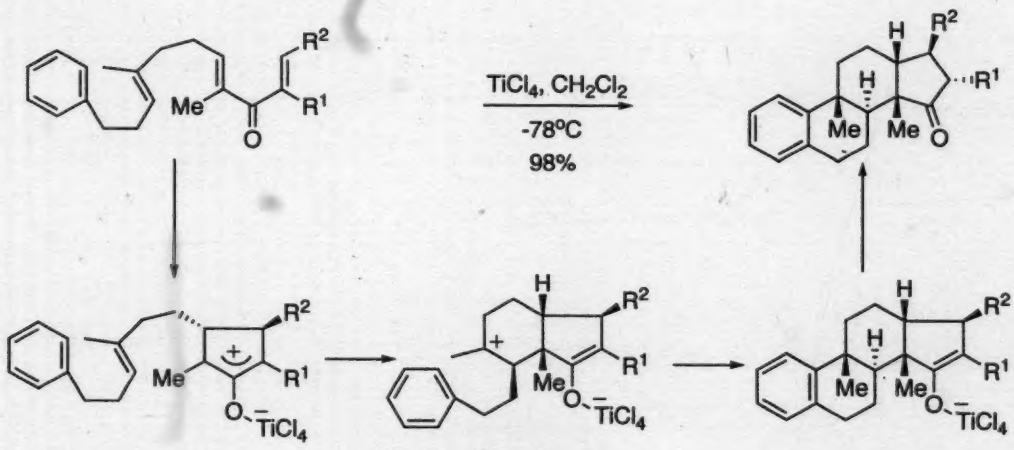
When a terminal alkene on a tethered chain was investigated, the reaction underwent a *6-endo* cyclization onto the oxyallyl cation to generate another key cationic intermediate shown in the brackets (Scheme 5). This cation can proceed through one of four reaction pathways: (1) elimination of a nearby proton; (2) hydride shift assisted by the Lewis-acid enolate; (3) formal [3+2] cycloaddition (only observed with BF_3); or (4) capture with chloride (only observed with $TiCl_4$). [33] In most cases, a mixture of products was obtained due to the different termination pathways, which indicated that substitution on the dienones was a very important factor in this reaction.



Scheme 5

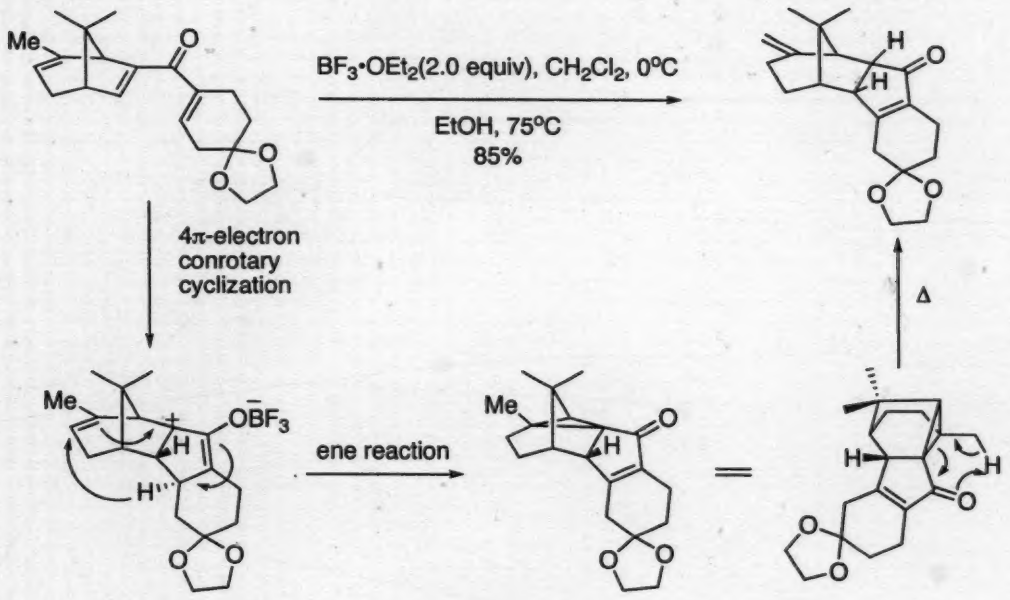
In light of these results, West and co-workers investigated a tandem cyclization of aryl trienones.[19] In this reaction, a tethered phenyl group terminated the resulting carbocation, which was generated *in situ* through a *6-endo* cyclization of an olefin to the initial Nazarov oxyallyl intermediate. The pendant alkene acted as a reactivity relay between the oxyallyl cation and the aryl moiety. This cationic olefin

polycyclization generated six stereocenters in one step and assembled the sterol skeleton and related structures with complete diastereoselectivity (Scheme 6). During studies on the reaction scope, the products from other reaction pathways, like elimination before or after the *6-endo* cyclization and hydride shift, were isolated in minor yields.



Scheme 6

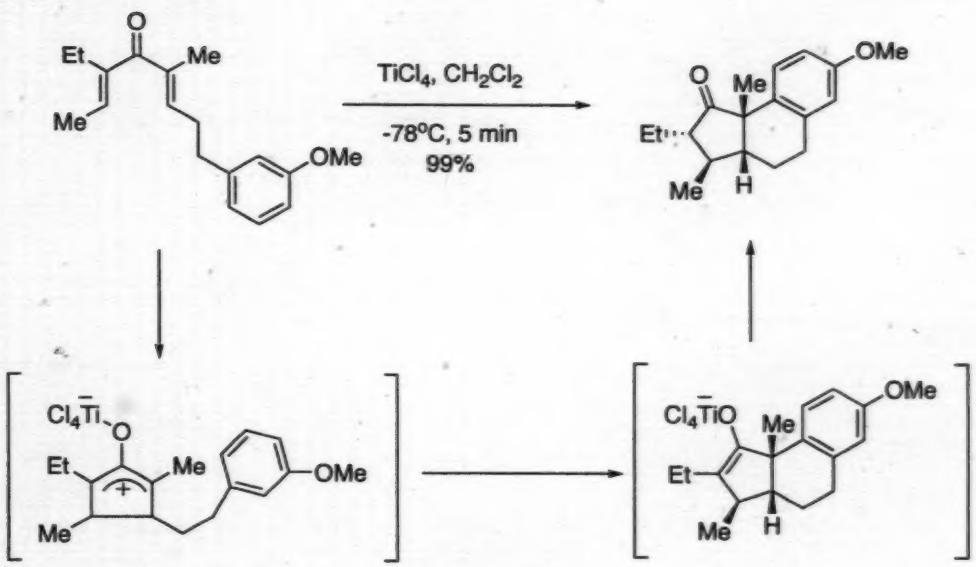
In 2005, West and co-workers reported another example of olefin trapping during the Nazarov cyclization.[34] When they investigated the Nazarov cyclization of bridged bicyclic dienones, a remote unconjugated alkene was found to participate in the the rearrangement of the Nazarov intermediate (Scheme 7). The following mechanism was proposed for formation of the external olefin: the nonconjugated alkene underwent intramolecular trapping of the oxyallyl cationic intermediate to generate polycyclic cyclopropyl ketone by 4π-electron cyclization and a direct ene-like reaction (or stepwise cation-olefin cyclization/hydride transfer). Thermal opening of cyclopropyl ketone then afforded the unexpected external olefin product. This process presents a convenient approach to assemble the skeleton of taxane natural products and their structural analogues.



Scheme 7

3.1.2 Intramolecular Trapping of the Nazarov Intermediate with Arenes

The success of intramolecular trapping with pendant olefins prompted West and co-worker to investigate the possibility of direct trapping with tethered aromatic moieties (Scheme 8).[21,22] Due to the inadequate nucleophilicity of an unsubstituted phenyl group, more electron-rich aromatic substrates were required for successful trapping. Compared to $BF_3 \cdot OEt_2$, $TiCl_4$ was found to be a more suitable Lewis acid, providing clean cyclization products in high yield. Substitution on the aromatic ring occurred at the more nucleophilic position (*para* to the methoxy) as expected. Also, attack on the cation always occurred *syn* to the tether while protonation of the enolate occurred on the convex face of *cis*-[5,6]-fused ring system. This trapping result furnished the stereoselective construction of arene-fused hydrindenones with four new stereocenters.

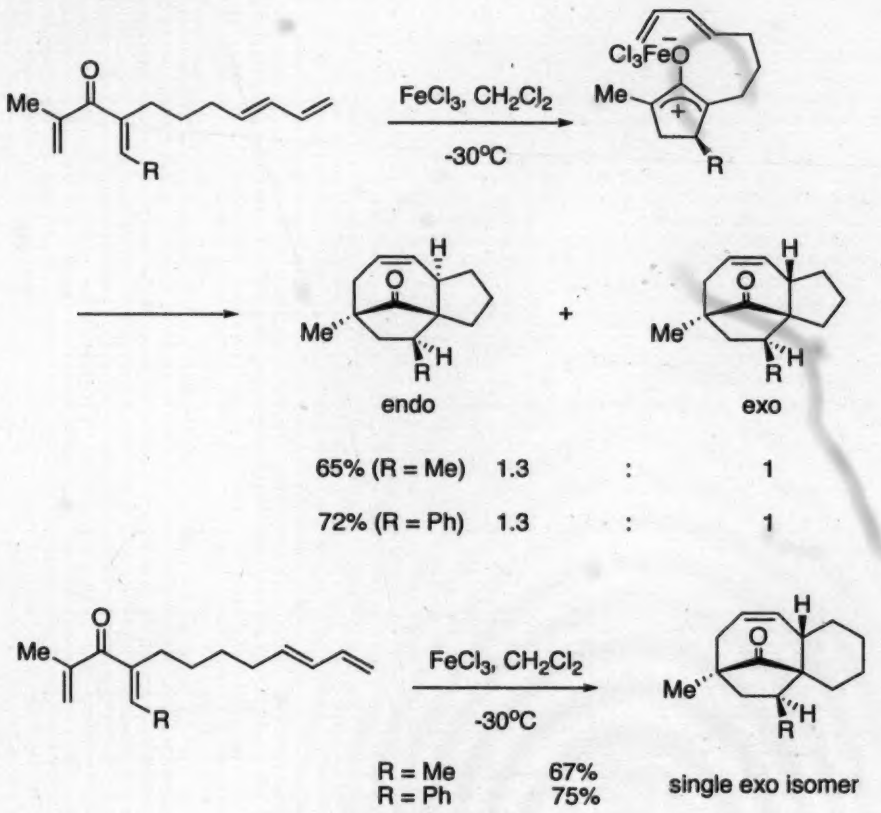


Scheme 8

3.1.3 Intramolecular/Intermolecular Trapping of the Nazarov Intermediate with Conjugated Dienes

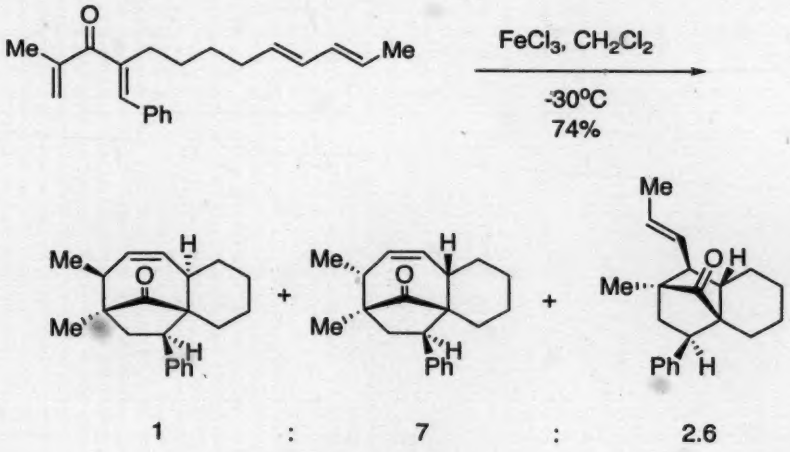
The oxyallyl cationic Nazarov intermediate has also been trapped by a pendent 1,3-diene (Scheme 9), which was found by West and co-workers.[23] This [4+3]-cycloaddition reaction would provide easy access to medium sized rings (eight-membered or seven-membered rings) or even larger rings. Harmata and Cha have also published the examples of intramolecular [4+3]-cycloadditions involving cyclic oxyallyls and conjugated dienes.[35,36] They generated cyclic oxyallyl cations using methods other than Nazarov electrocyclization. Among a variety of Lewis acids, a catalytic amount of $FeCl_3$ was found to effect the Nazarov cyclization successfully. When published, this reaction was one of the few cases of efficient catalysis of the Nazarov cyclication. When there were three carbons separating the dienone and tethered diene, the 1,3-diene preferred to approach the oxyallyl from the less hindered face, resulting in complete diastereofacial selectivity, but a modest ratio of *endo* vs *exo* isomers. Replacement of the phenyl substituent with methyl had no effect on the ratio, and the reaction proceeded in a lower yield. However, with a four-carbon

tether, complete facial selectivity and exclusive *exo* selectivity were observed, providing a single isomer.



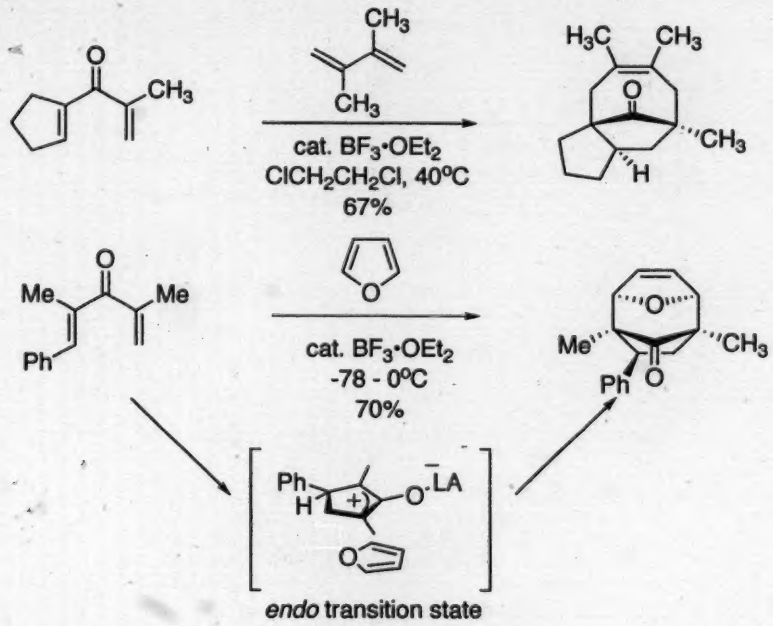
Scheme 9

When the substrate contained an additional methyl substituent on the 1,3-diene, three products were isolated from the standard reaction conditions and a better ratio of *exo* vs *endo* isomers was obtained (Scheme 10). The additional [3+2] adduct was proposed to arise from trapping of the oxyallyl cation with the proximal olefin to provide an allylic carbocation. Finally, closure of the enolate onto the allylic carbocation would form the bridged ketone product. This demonstrates another example of trapping the Nazarov intermediate with olefins.



Scheme 10

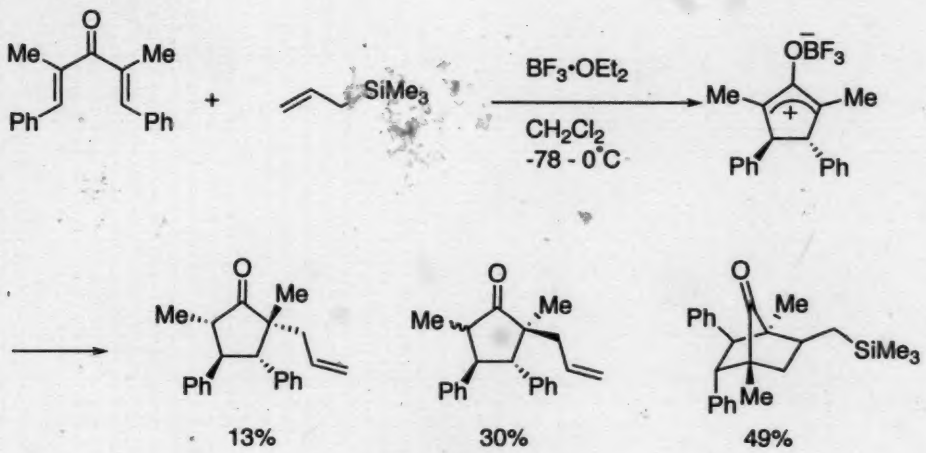
[4+3] capture of the Nazarov intermediate with a 1,3-diene could also occur in an intermolecular manner (Scheme11).[24] The 1,3-diene could be acyclic or cyclic, such as 2,3-dimethylbutadiene, isoprene, or furan. Trapping with furan proceeded *via* the *endo* transition state, and complete facial selectivity was obtained due to the effect of substituents on the oxyallyl cation. These results suggest an efficient approach to cyclooctanoids, which commonly exist in natural products.



Scheme 11

3.1.4 Intermolecular Trapping of Nazarov Intermediate with Allysilane

Due to the well-known nucleophilic reactivity and Lewis acid tolerance of allyl silanes, West and co-workers examined them as effective trapping reagents in the interrupted Nazarov reaction (Scheme 12).[25] To their surprise, when allyl trimethylsilane was used, simple allylation products along with the unexpected bicyclo[2.2.1]heptanones were isolated in a 1:1 ratio. To form the [3+2] cycloadduct, the bicycol[2.2.1]heptanones, the β-silyl cation is trapped with the enolate carbon rather than undergoing desilylation. This process is similar to the trapping of oxyallyl cations with simple alkenes and is the first example of intermolecular trapping by a carbon nucleophile. The use of bulky allyl triisopropylsilane in this reaction increased the formation of the [3+2] cycloadduct. In the unsymmetrical cases, addition of the allylsilane occurred at the less substituted end of the oxyallyl cation due to steric effects.

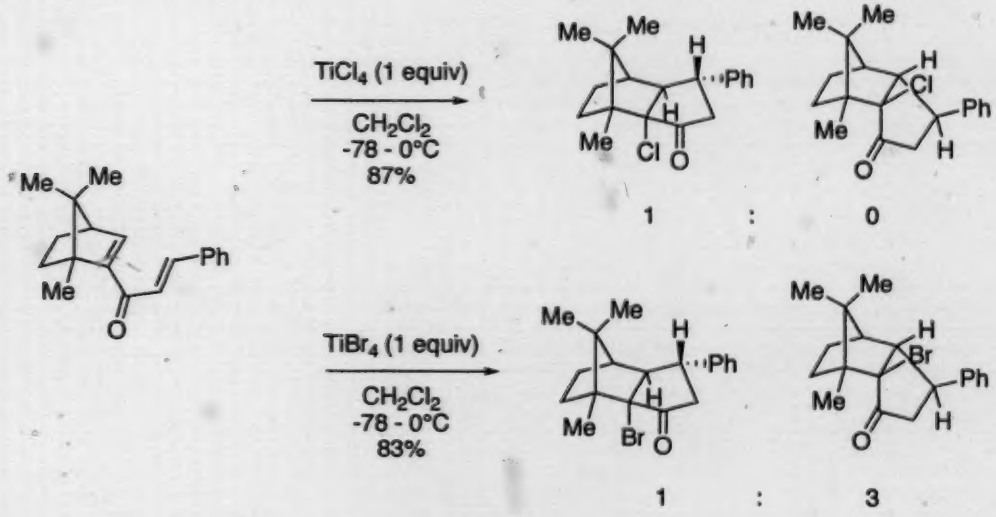


Scheme 12

3.1.5 Intermolecular Trapping of the Nazarov Intermediate with Halide Anions

In the Interrupted Nazarov Reaction, halides (Cl, Br, I) have been found to behave similarly to other trapping sources (Scheme 13).[27] In the Nazarov reaction of bicyclic dienones, $TiCl_4$ functioned as the Lewis acid to initiate conrotatary cyclization. Meanwhile, $TiCl_4$ also supplied a Cl^- to intercept the oxyallyl cationic

intermediate. In the example shown below, trapping with chloride resulted in only *exo* isomers. When $TiBr_4$ was used in place of $TiCl_4$, bromide adducts were obtained in a ratio of 1:3. The major product was the *endo* isomer. It is not clear why these two cases resulted in different electrocyclization diastereoselectivity. TiI_4 and TiF_4 were also examined, however, no iodide and fluoride trapping products were observed.

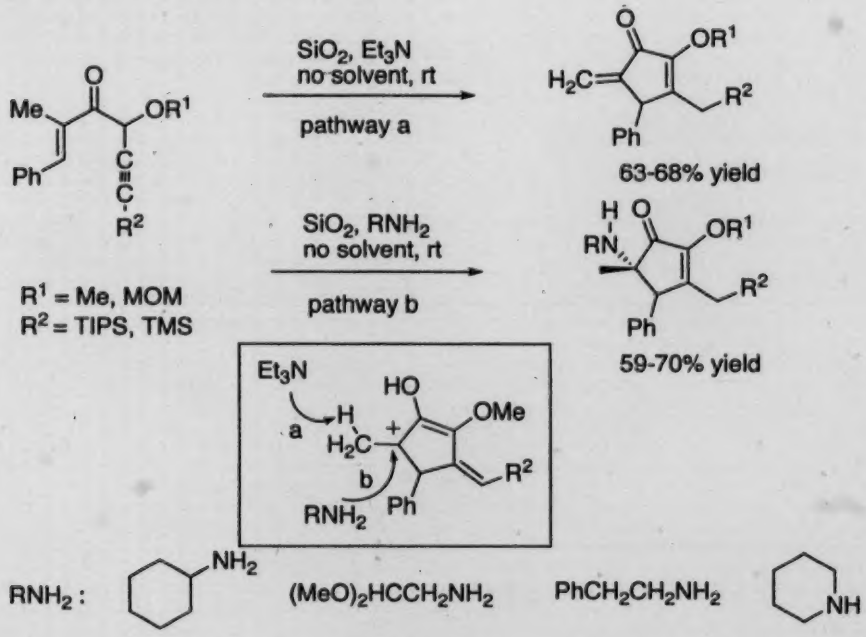


Scheme 13

3.1.6 Intermolecular Trapping of the Nazarov Intermediate with Amines

Recently, Tius and co-workers described the first intermolecular trapping involving C-N bond formation in the interrupted Nazarov reaction (Scheme 14).[37] When the Nazarov precursors were treated with activated dry silica gel in the presence of triethylamine, cyclopentenone products were isolated. When primary or secondary amines were utilized, α-amino ketone products were obtained. The key cationic intermediate proposed for the reaction is shown in the box. In pathway a, the tertiary amine deprotonates next to the carbocation to generate the observed cyclopentenones. In pathway b, nucleophilic trapping with primary and secondary amines took place more rapidly than deprotonation. In order to optimize this trapping reaction it is run in the absence of solvent. In the presence of solvent, proton loss

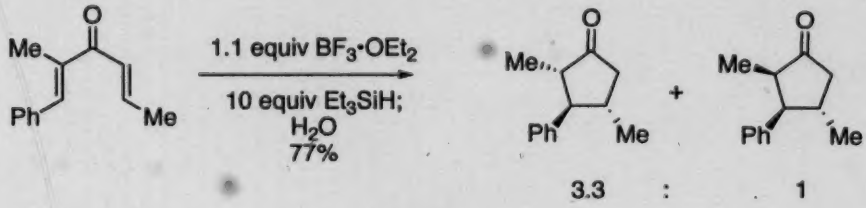
from the cationic intermediate occurred readily to provide decreased yields of the desired amino ketone products.



Scheme 14

3.1.7 Intermolecular Trapping of the Nazarov Intermediate with Hydride: The Reductive Nazarov Cyclization with Triethylsilane

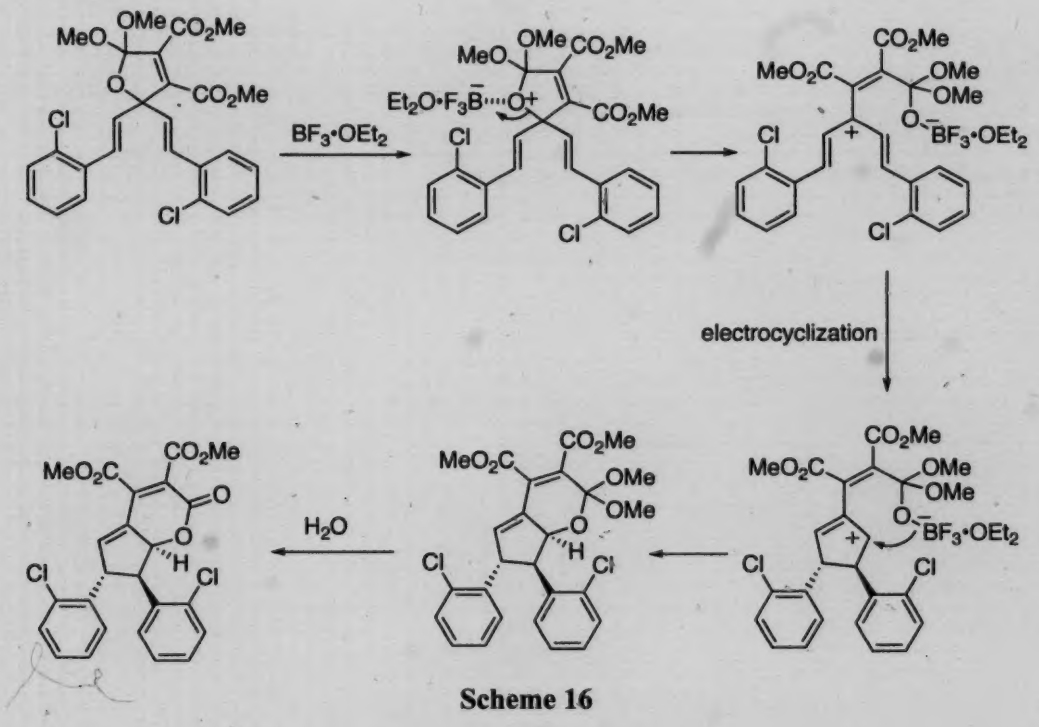
Triethylsilane could also be used to terminate the oxyallyl cationic intermediate formed in the Nazarov cyclization through intermolecular hydride transfer (Scheme 15).[26] Triethylsilane is a useful hydride source in these reactions because it is tolerant to Lewis acid. At least two equivalents of silane were required and in some cases a catalytic amount of Lewis acid could be used. Depending on the work-up conditions, either cyclopentanones or silyl enol ethers could be isolated.



Scheme 15

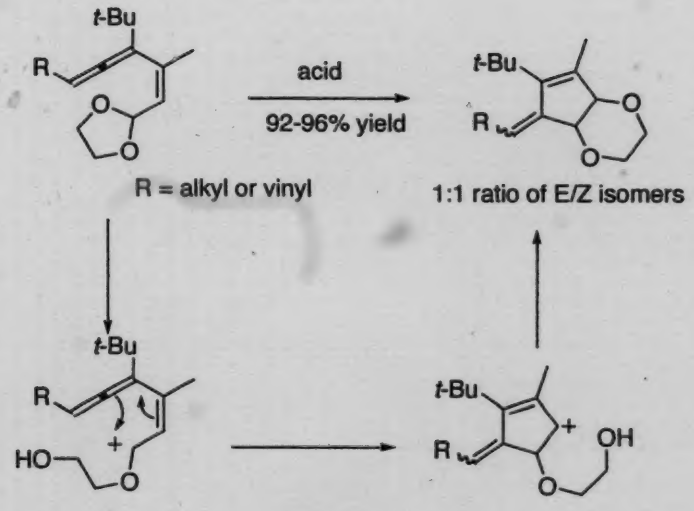
3.1.8 Intramolecular Trapping of the Nazarov Intermediate with Oxygen Nucleophiles

Nair has described an interrupted Nazarov cyclization involving trapping with oxygen nuleophiles (Scheme 16).[38] In this example, a cyclic orthoester was opened with $BF_3{\cdot}OEt_2$ to afford a pentadienyl cation. The pentadienyl cation then underwent 4π-electrocyclization to generate an allyl cationic intermediate. The resulting allyl cation was trapped by the pendant orthoester borate to provide a bicyclic product. Under the work-up conditions, the bicyclic product was readily converted to a lactone.



Scheme 16

De Lera and co-workers reported another oxygen-interrupted reaction (Scheme 17).[39] In this case, activation of the Z-vinyl acetal by protic or Lewis acid resulted in formation of a pentadienyl cation. An efficient cyclization then occurred to generate allyl cationic intermediate, which was captured by the pendant oxygen. The resulting dioxane product was obtained as a 1:1 mixture of E/Z exocyclic olefins.



Scheme 17

3.1.9 Summary

The oxyallyl cationic intermediate that results from the conrotatory Nazarov cyclization has been successfully trapped by a number of carbon nucleophiles: (1) tethered alkenes; (2) tethered arenes; (3) tethered acyclic or cyclic 1,3-dienes; and (4) allylsilanes. Aside from the carbon traps, other nucleophiles (hydride, halide, oxygen, nitrogen) have also been found to capture the oxyallyl cation. These examples of the interrupted Nazarov reaction highlight the formation of new carbon-carbon bonds or carbon-heteroatom bonds and the preservation of stereochemistry that was generated in the initial electrocyclization.

3.2 Background

In recent years, numerous examples have been reported, wherein the oxyallyl cationic intermediate generated during the Nazarov cyclization have been intercepted by different nucleophiles. In light of these developments, our group has become interested in trapping the oxyallyl cation with electron-rich organic azides. Cycloaddition and rearrangement chemistry are two major fields associated with modern azide chemistry. The chemical reactivity of azides can be explained by their

polar mesomeric structures. There are four major resonance contributors for an azide group (Figure 1). Loss of nitrogen gas to afford rearrangement products can be attributed to dipolar structure **c**. 1,3-Dipolar structure **d** can be used to explain the ease of cycloaddition of azides with dipolarophiles. Structure **d** can also explain why azides react with electron-deficient compounds (electrophiles) at N1 and electron-rich compounds (nucleophiles) at N3.

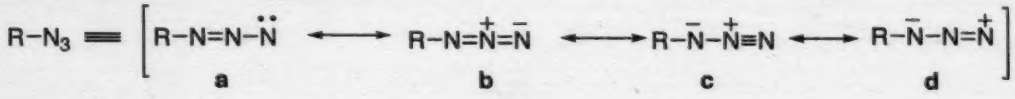


Figure 1. Resonance Forms of Azide

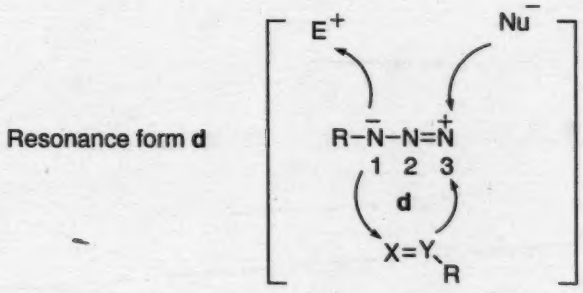
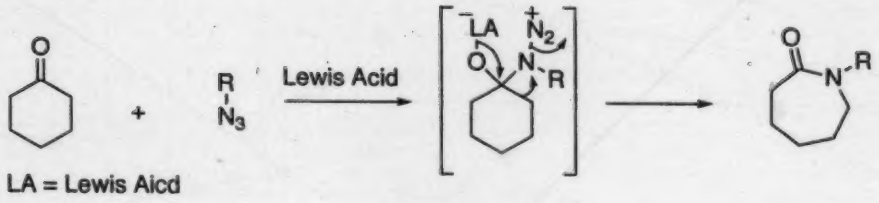


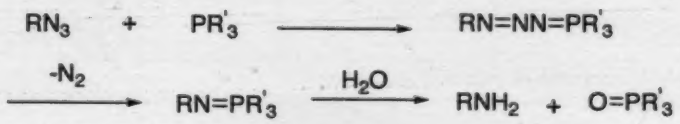
Figure 2. Reactivity of Azides

Organic azides can react with suitable electrophiles such as carbon electrophiles, protons, and boranes. The reactions always occur with attack from N1 position to form an amine-substituted diazonium ion. The resulting diazonium ion can then lose nitrogen to generate an eletron-deficient nitrenium ion which can be involved in rearrangement process. The Boyer reaction is one example of such a rearrangement. The reaction of aliphatic azides with ketones in the presence of a Brønsted acid results in *N*-alkylated amides or lactams.[40] Aubé and co-workers observed that the Boyer reaction could be done more efficiently in the presence of a Lewis acid (Scheme 18).[41,42]



Scheme 18

Organic azides can also readily react with nucleophiles at the N3 position. One of the most important applications of this chemistry is the Staudinger reduction,[43,44] which involves the attack of azides by phosphorus nucleophiles (Scheme 19). This reaction proceeds through a phosphazine intermediate, which is generated by the attack of phosphorus nucleophiles to the terminal nitrogen of an azide. Subsequent loss of nitrogen from the phosphazine intermediate results in an iminophosphorane, which can be hydrolyzed to the primary amine.

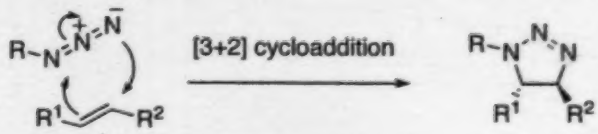


Scheme 19

3.2.1 Cycloaddition of Azides

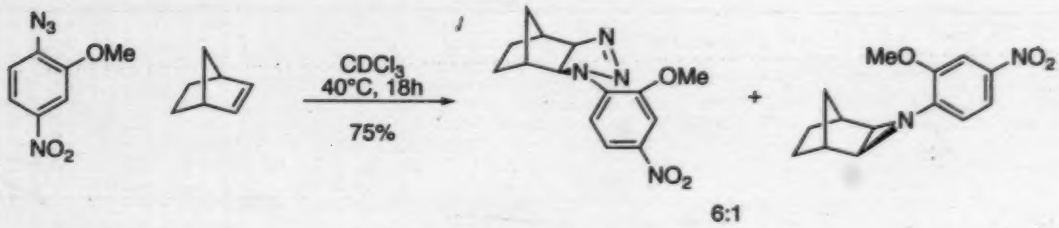
The cycloaddition of 1,3-dipoles to dipolarophiles, known as Huisgen reaction,[45] is an approach used to synthesize 5-membered heterocycles. Dipolarophiles can be alkenes, alkynes, and molecules that possess related heteroatom functional groups (such as carbonyls and nitriles). 1,3-Dipolar compounds contain one or more heteroatoms and should have at least one charged dipolar mesomeric structure. Azides, nitrile oxides and diazoalkanes are common 1,3-dipolar compounds. The reaction is a [2s+4s] cycloaddition similar to the Diels-Alder reaction. The 2π electron contribution from the dipolarophile reacts with the

4π electrons of the 1,3-dipolar compound to undergo a concerted, suprafacial process, generating a 5-membered heterocycle with stereospecifity (Scheme 20).



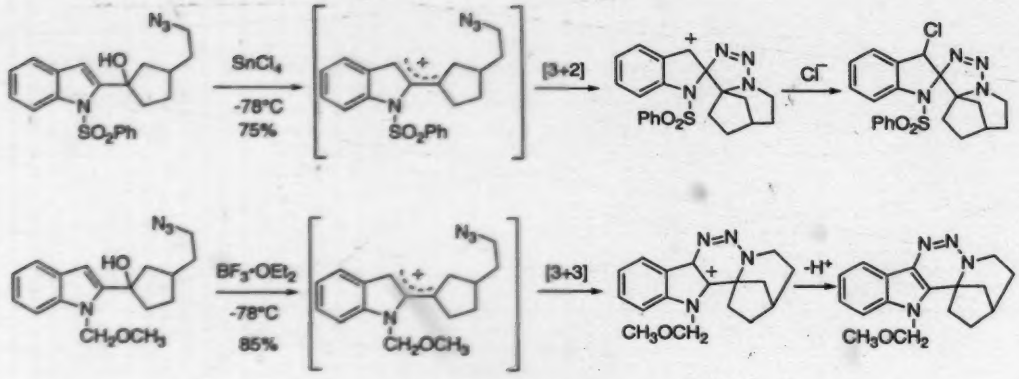
Scheme 20

Organoazides can react with both electron-deficient alkenes and electron-rich alkenes such as enol ethers and enamines. The cycloaddition of azides to strained alkenes is shown below (Scheme 21). The reaction of aryl azide with norbornene at 40°C resulted in a mixture of triazoline and aziridine products in a ratio of 6:1.[46] It was believed that the triazoline was initially formed and could undergo further rearrangement to give the aziridine product.



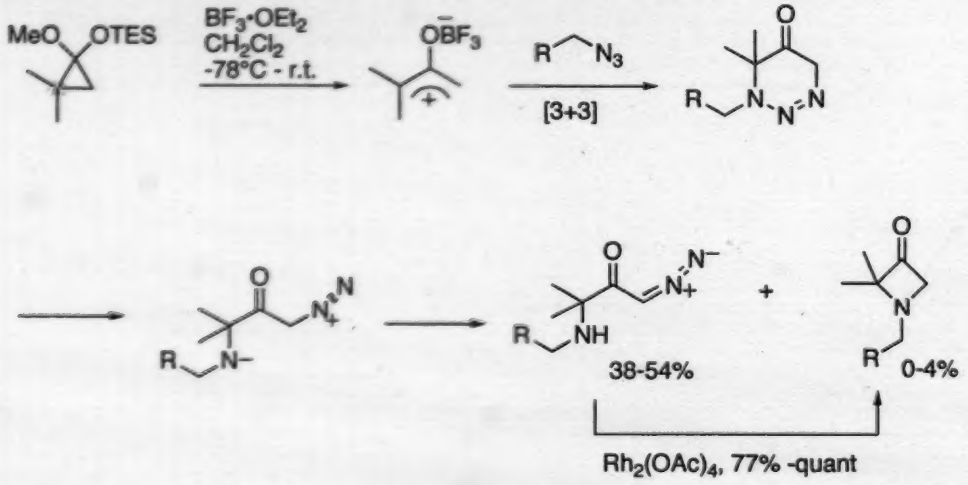
Scheme 21

Pearson and co-workers observed that other π-systems such as allyl cations could also react with organo azides.[47] The reaction proceeded at low temperature in the presence of a Lewis acid. Depending on the substitution on nitrogen (*N*-sulfonyl vs *N*-alkyl), either [3+2] or [3+3] cycloaddition products could be obtained (Scheme 22). The regioselectivity may lie in the stability of the cation generated after the cycloaddition. Trapping or elimination of the resulting intermediate gave the observed triazine derivatives. It appears that an electron releasing substituent (*N*-alkyl) is needed to stabilize the adjacent carbocation, in order to form the [3+3] cycloadduct.



Scheme 22

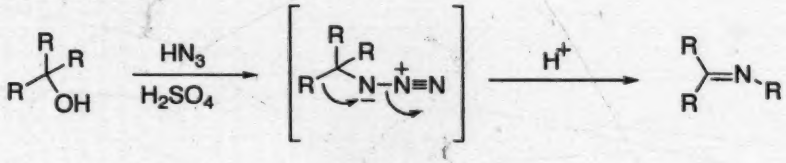
Recently, Desai and Aubé reported the reaction of alkyl azides with triethyl(1-methoxy-2,2-dimethyl-cyclopropoxy)silane, which resulted in a series of α-amino-α'-diazomethyl ketones in moderate yields (Scheme 23).[48] The mechanism of this reaction involves the generation of an oxyallyl cation by opening a cyclopropane ring in the presence of a Lewis acid. The resulting oxyallyl cation can then undergo a concerted or stepwise [3+3] cycloaddition with an an alkyl azide to provide triazine products. Ring opening of the cycloadduct, followed by proton transfer affords the diazoketone as a major product. The minor 3-azetidinones may arise from the direct cyclization after ring opening of the triazine. Treatment of these diazoketones with $Rh_2(OAc)_4$ resulted in 3-azetidinones in good to excellent yield.



Scheme 23

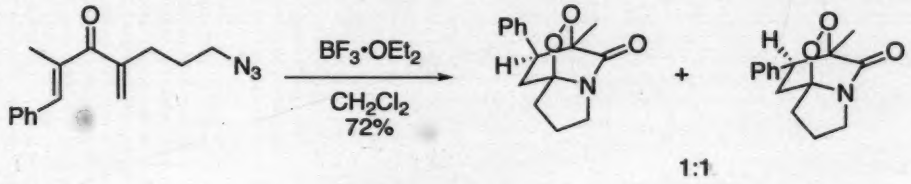
3.2.2 Rearrangement

Organic azides are also commonly used in rearrangement reactions, such as the Curtius rearrangement, Schmidt rearrangement (Scheme 24), Boyer, and Boyer-Aubé rearrangements (Scheme 18). In the Schmidt rearrangement, the key intermediate, shown in the brackets, undergoes rearrangement with extrusion of N_2 in a concerted manner. Depending on the R substituent, the Schmidt reaction can be used to produce amines, nitriles, amides or imines.

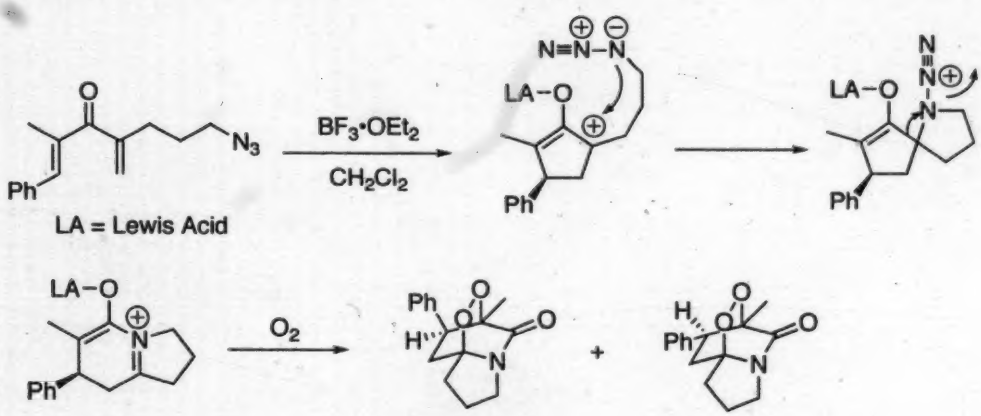


Scheme 24

West and co-workers have investigated the intramolecular trapping of the Nazarov intermediate with a three-carbon tethered azide (Scheme 25).[49] The peroxy-bridged indolizidinones were isolated at a 1:1 ratio. The internal nitrogen on the azide group acts as a nucleophile to attack Nazarov intermediated which is generated *in situ*. Then a Schmidt type rearrangement occurs to provide the key 1,4-dipole intermediate, which then undergoes reaction with atmospheric oxygen (Scheme 26).



Scheme 25

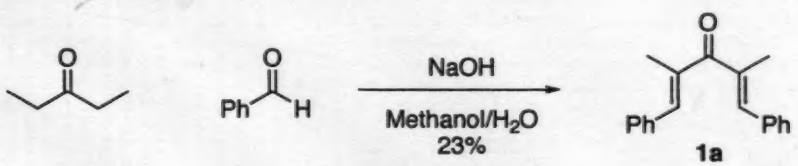


Scheme 26

The intramolecular trapping attempts were successful; however, the intermolecular version had yet to be examined. It is trying because intermolecuar trapping can prepare library of nitrogen heterocycles from simple precursors. A multistep route was required for the synthesis of the azidodienone substrates in the intramolecular trapping. Following is a discussion on our efforts in the area of intermolecular trapping of the Nazarov intermediate by organic azides.

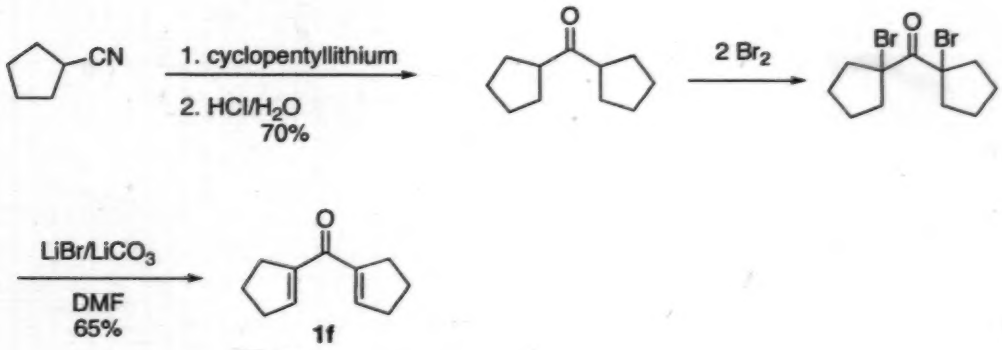
3.3 Substrate Preparation

In order to investigate the intermolecular version of this reaction, various dienones and organoazides were prepared from readily available starting materials. The first dienone to be examined was dibenzylidenepentanone **1a,** since **1a** had previously shown exceptional reactivity toward electrocyclic closure, even at low temperature.[24-26] **1a** was prepared in a low yield from the condensation of 3-pentanone with benzaldehyde in basic medium (Scheme 27).[50,51]



Scheme 27

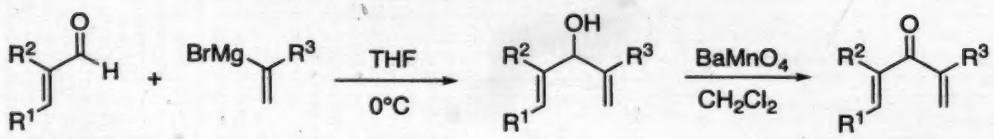
1,1'-Dicyclopentenyl ketone,[52] **1f**, was prepared from cyclopentanecarbonitrile by a sequence of three reactions (Scheme 28). Treatment of cyclopentanecarbonitrile with cyclopentyllithium (prepared from lithium and cyclopentylbromide) followed by hydrolysis resulted in dicyclopentyl ketone in 70% yield. α-Dibromination of dicyclopentyl ketone resulted in 1,1'-dibromodicyclopentyl ketone which was used directly in the next step without purification. β-Elimination occurred in the presence of lithium carbonate to provide the desired 1,1'-dicyclopentenyl ketone, **1f**, in 65% yield.



Scheme 28

Other dienones were prepared by a two step sequence: (1) 1,2-addition of vinyl or isopropenyl Grignard reagent to either α-methyl-*trans*-cinnamaldehyde or 1-cyclohexene-1-carboxaldehyde; and (2) oxidation of the resulting alcohol by barium manganate (Table 1). 2-Bromopropene was used to prepare the isopropenyl Grignard reagent. Barium manganate is a mild and effective oxidant for the conversion of dienols to dienones.[53,54] However, the oxidation step was slow and required at least 3 equivalents of barium manganate to drive the reaction to completion.

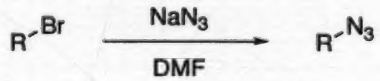
Table 1. Formations of Dienone Substrates



entry	substrate	R^1	R^2	R^3	overall yield (%)
1	**1b**	Ph	Me	Me	48
2	**1c**	Ph	Me	H	55
3	**1d**		$(CH_2)_4$	Me	50
4	**1e**		$(CH_2)_4$	H	44

Three different alkyl azides were prepared from readily available alkyl bromides (Table 2). Treatment of the alkyl bromide (benzyl, phenylpropyl, phenylpropenyl) with sodium azide in DMF resulted in the desired alkyl azides in near quantitative yields.

Table 2. Synthesis of Organoazide Substrates



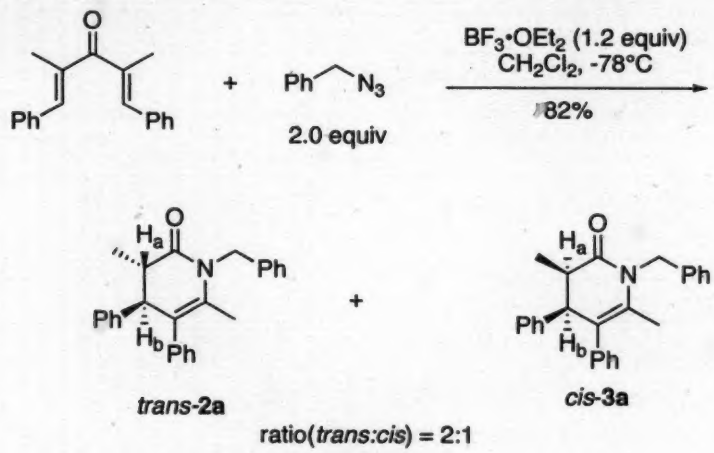
entry	substrate	R	yield (%)
1	**8**	CH_2Ph	98
2	**9**	$(CH_2)_3Ph$	97
3	**10**	$CH_2CH{=}CHPh$	98

3.4 Results and Discussion

3.4.1 Preliminary Results

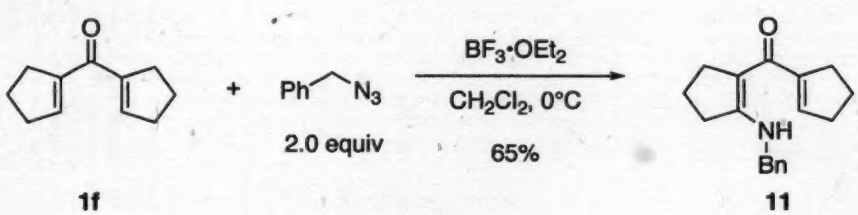
In our initial studies, treatment of **1a** with two equivalents of benzyl azide in the presence of 1.2 equivalents of $BF_3{\cdot}OEt_2$ at low temperature resulted in two diastereoisomers in a ratio of 2:1 (Scheme 29). The reaction went to completion in 10 minutes, as monitored by TLC. Further investigation of this reaction led to the

discovery that fewer equivalents of benzyl azide provided a complex mixture of products. Also, when using a catalytic amount of $BF_3{\cdot}OEt_2$, the reaction proceeded very slowly. It seemed that an excess of benzyl azide and Lewis acid were necessary for this reaction to occur. Based on these results, it was decided that two equivalents of alkyl azide and 1.2 equivalents of $BF_3{\cdot}OEt_2$ would be used for all subsequent examples in this investigation.



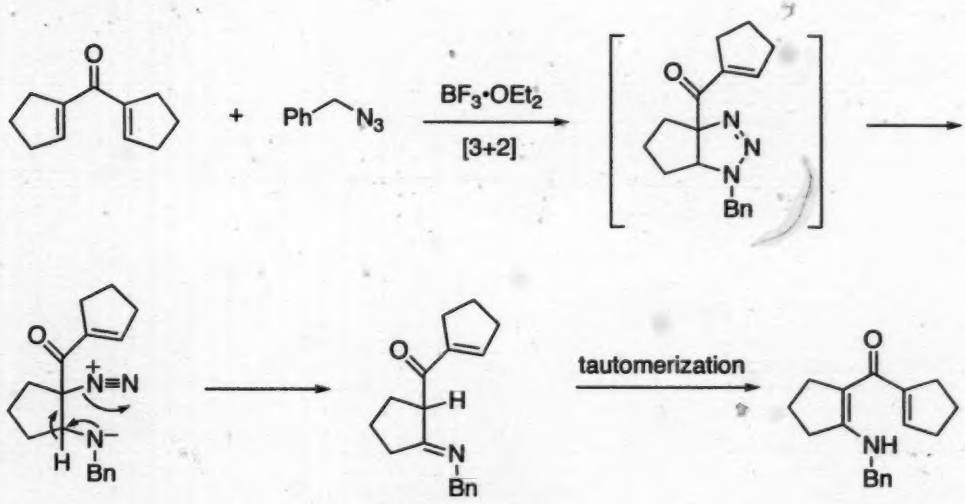
Scheme 29

The second dienone to be examined was **1f** (Scheme 30). If the expected trapping were to occurr, it would furnish an interesting polycyclic ring system. Unfortunately, there was no reaction at -78°C when **1f** was treated with benzyl azide under the previously optimized reaction conditions. When the mixture was warmed up to room temperature for two hours, a reaction observed by TLC and the reaction was quenched. Compound **11** was isolated as a single product instead of the desired trapping products.



Scheme 30

To explain this result, a proposed mechanism for the formation of **11** is shown below (Scheme 31). The unsaturated ketone could first undergo a [3+2] cycloaddition reaction with azide in the presence of Lewis acid to generate a triazoline intermediate. The nonstabilized triazene,[55] could then open it open an amidodiazonium betaine under the reaction conditions. The resulting intermediate could either undergo a [1,2]-hydride shift or a ring contraction to provide a four-membered ring. On this substrate, hydride migration would be more likely to occur than ring contraction. Tautomerization would afford the endocyclic enaminone. This type of mechanism has been proposed by Aubé and co-workers.[56] Their work involved a series of reactions of unsaturated ketones with alkyl azides in a similar reaction pathway.

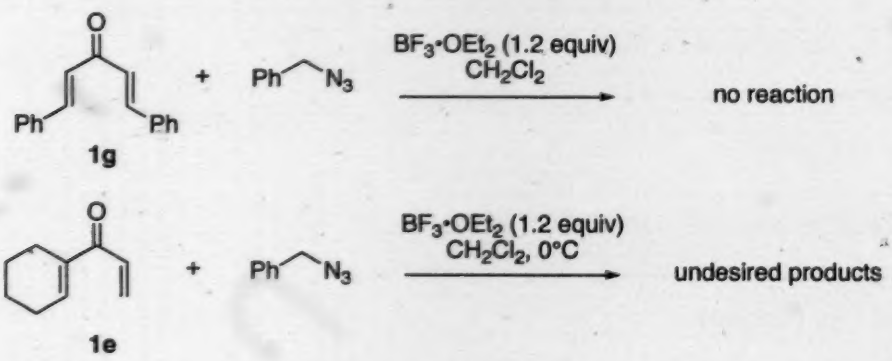


Scheme 31

Based on the isolated product **11**, it is possible that this alkyl azide and the dienone undergo a [3+2] cycloaddition before the Nazarov cyclization of the dienone occurs. In this example, dicyclopentenyl ketone **1f** is less reactive than **1a**, so a higher temperature is needed to make the Nazarov cyclization occur. However, when the reaction mixture reaches a necessary temperature, the substrate undergoes a [3+2] cycloaddition instead to generate the conjugate addition product. This result

demonstrates a clear drawback of this azide trapping reaction. Since there is a competing reaction, the dienone substrates must be reactive enough to do the electrocyclization before the [3+2] cycloaddition can occur.

Another two unsuccessful examples involve substrates **1g** and **1e** (Scheme 32). Dibenzylideneacetone did not result in any product formation, even at room temperature. This may be due to competing electrocyclization and [3+2] cycloaddition reactions. When **1e** was used as the substrate, it was consumed at 0°C; however, it was not a clean reaction and the products isolated were not the expected ones. These reactions were not investigated further because numerous successful examples were discovered concurrently, employing other reactants.



Scheme 32

Three other dienone substrates were found to react with benzyl azide succesfully to provide the trapping products in moderate to good yield. These dienones were also combined with two different alkyl azides to examine the scope of this reaction. Fortunately, all of the reactions generated the expected products (Table 3). Dienone **1a** also underwent an interrupted Nazarov in the presence of 3-phenylpropyl azide and cinnamyl azide (entry 2 and 3) to give **4a/5a** and **6a/7a**, respectively, in similar ratios as **2a/3a** (entry 1). Unsymmetrically substituted dienones **1b-d** (entry 4 to 12) were also examined with several alkyl azides. Moderate to good yields were obtained in all of these examples. Dienone **1b** (entry 4 to 6) also reacted with different azides at -78°C to afford expected trapping products in good yields; however, in this case only the *trans* isomer was observed after

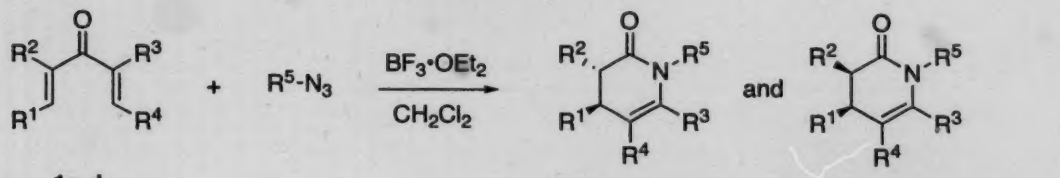
purification. Unlike dienones **1a** and **1b**, dienone **1c** (entry 7 to 9) required warming to 0°C to initiate the reaction and proceeded in moderate yields. We attribute this result to a high barrier for Nazarov cyclization due to the formation of a relatively less stable oxyallyl carbocation compared to the dienones **1a** and **1b** (entry 1 to 6). Due to the strain associated with the resulting bicyclo[4.3.0]cation, dienone **1d** (entry 10 to 12) also required higher reaction temperatures for Nazarov cyclization. However, in this case the good yields can be attributed to the fact that the oxyallyl cation was stable enough to have a longer lifetime which allowed trapping to occur. Interestingly, only *trans* isomers were observed for dienones **1b** and **1c** (entry 4 to 9) in the interrupted Nazarov reaction. The stereoselectivity of this reaction prompted us to consider the reaction mechanism in a different way. There are two possible reaction pathways: one would generate a mixture of two isomers, the other would give absolute *trans* isomers.

Regioselectivity was also observed with unsymmetric dienones **1b-1d** (entry 1 to 12). The alkyl azides added to the oxyallyl cation of the Nazarov intermediate exclusively from the less hindered side.

3.4.2 Structure Determination

The relative stereochemistry of two diastereoisomers **2a/3a** was determined by comparing the coupling constants of H_a and H_b. In one isomer, H_a and H_b has a large coupling constant (J_{ab} = 7.0 Hz). In the other isomer, H_a and H_b has a small coupling constant (J_{ab} = 2.0 Hz) (Figure 3). Standard axial/equatorial distinction may not apply to H_a and H_b since **2a/3a** has three sp^2 centers. But we suppose H_a and H_b are in the pseudoaxial and pseudoequatorial. According to the Karplus curve, two axial protons share a large coupling constant while equatorial and axial protons will share a small coupling constant. That means the isomer that possesses a large *J* value is the *trans* product, and the isomer that has the small *J* value is the *cis* product. Also, compared with literature values for *cis/trans* dihydropyridones, they are matched.[57-59]

Table 3. Intermolecular Interrupted Nazorov Cyclization of Dienones with Simple Azides



1a-d

2 (R_5 = Bn) **3** (R_5 = Bn)

4 (R_5 = $(CH_2)_3Ph$) **5** (R_5 = $(CH_2)_3Ph$)

6 (R_5 = $CH_2CHCHPh$) **7** (R_5 = $CH_2CHCHPh$)

entry	dienone	R^1	R^2	R^3	R^4	R^5	temperature/time	products (% yield)
1	**1a**	Ph	Me	Me	Ph	CH_2Ph	-78°C/10 min	**2a + 3a** (82; 2:1)
2	**1a**	Ph	Me	Me	Ph	$(CH_2)_3Ph$	-78°C/10 min	**4a + 5a** (78;2.3:1)
3	**1a**	Ph	Me	Me	Ph	$CH_2CHCHPh$	-78°C/10 min	**6a + 7a** (85; 2:1)
4	**1b**	Ph	Me	Me	H	CH_2Ph	-78°C/0.5 h	**2b** (75)
5	**1b**	Ph	Me	Me	H	$(CH_2)_3Ph$	-78°C/0.5 h	**4b** (80)
6	**1b**	Ph	Me	Me	H	$CH_2CHCHPh$	-78°C/0.5 h	**6b** (72)
7	**1c**	Ph	Me	H	H	CH_2Ph	0°C/1 h	**2c** (62)
8	**1c**	Ph	Me	H	H	$(CH_2)_3Ph$	0°C/1 h	**4c** (40)
9	**1c**	Ph	Me	H	H	$CH_2CHCHPh$	0°C/1 h	**6c** (43)
10	**1d**	$(CH_2)_4$		Me	H	CH_2Ph	0°C/ 0.5 h	**2d + 3d** (80; 2:1)
11	**1d**	$(CH_2)_4$		Me	H	$(CH_2)_3Ph$	0°C/ 0.5 h	**4d + 5d** (70; 3:1)
12	**1d**	$(CH_2)_4$		Me	H	$CH_2CHCHPh$	0°C/ 0.5 h	**6d +7d** (73;2.5:1)

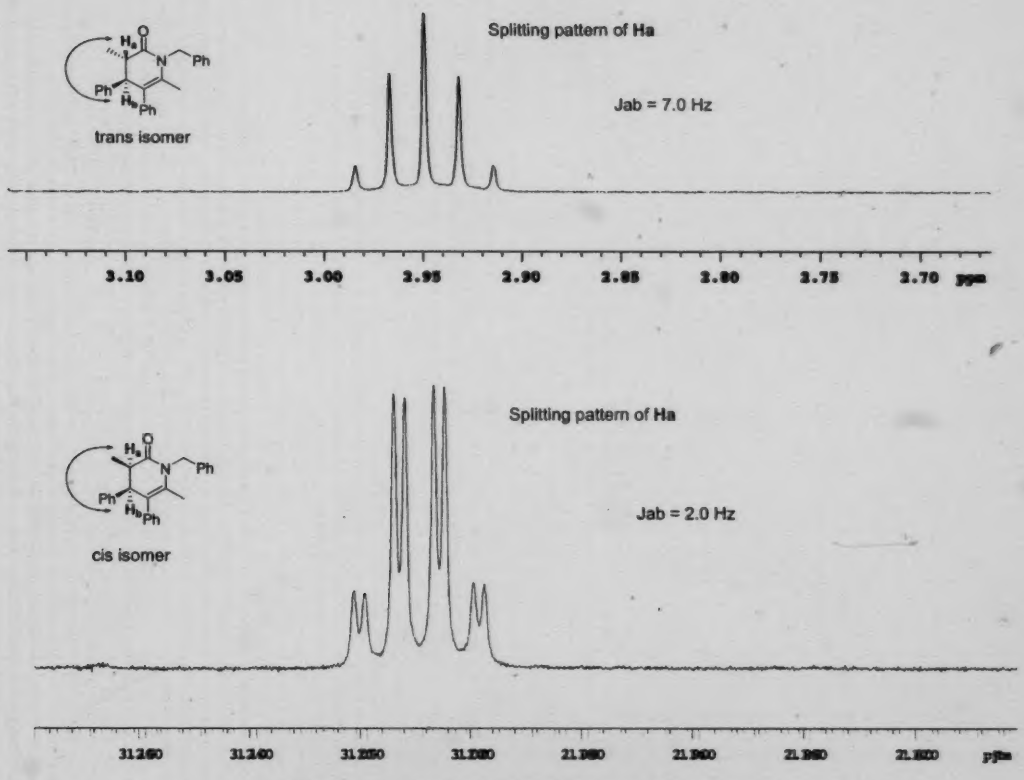


Figure 3. Splitting Patterns of 2a/3a

The relative conformations of **2d/3d** were also determined by analysis of the coupling constants of H_a, although they are not real decalins. For the *trans* decalins, both H_a and H_b should be in axial positions. H_a would display three couplings, two large couplings (axial - axial relationships) and one small coupling (axial - equatorial relationship). For the *cis* decalins, either H_a or H_b is in the axial position, but not both since they cannot occupy axial positions at the same time. As a result, there may be two or even three small couplings for H_a depending on the conformation of *cis* decalin.

The assignment of H_a in both isomers was first solved by 2D NMR analyses. The proton peaks are separated well in C_6D_6 compared with other deuterium solvents. Since H_a and H_b are close each other, an NOE experiment would not be useful for assignment of these protons. Only coupling constants were needed to determine the

relative stereochemistry (Figure 4). In the *trans* isomer, H_a was split into a *ddd* pattern in which the *J* values were 3.5, 11.7, and 15.1 Hz. On the contrary, the splitting pattern for H_a in the *cis* isomer was an apparent quartet ($J = 4.6$ Hz).

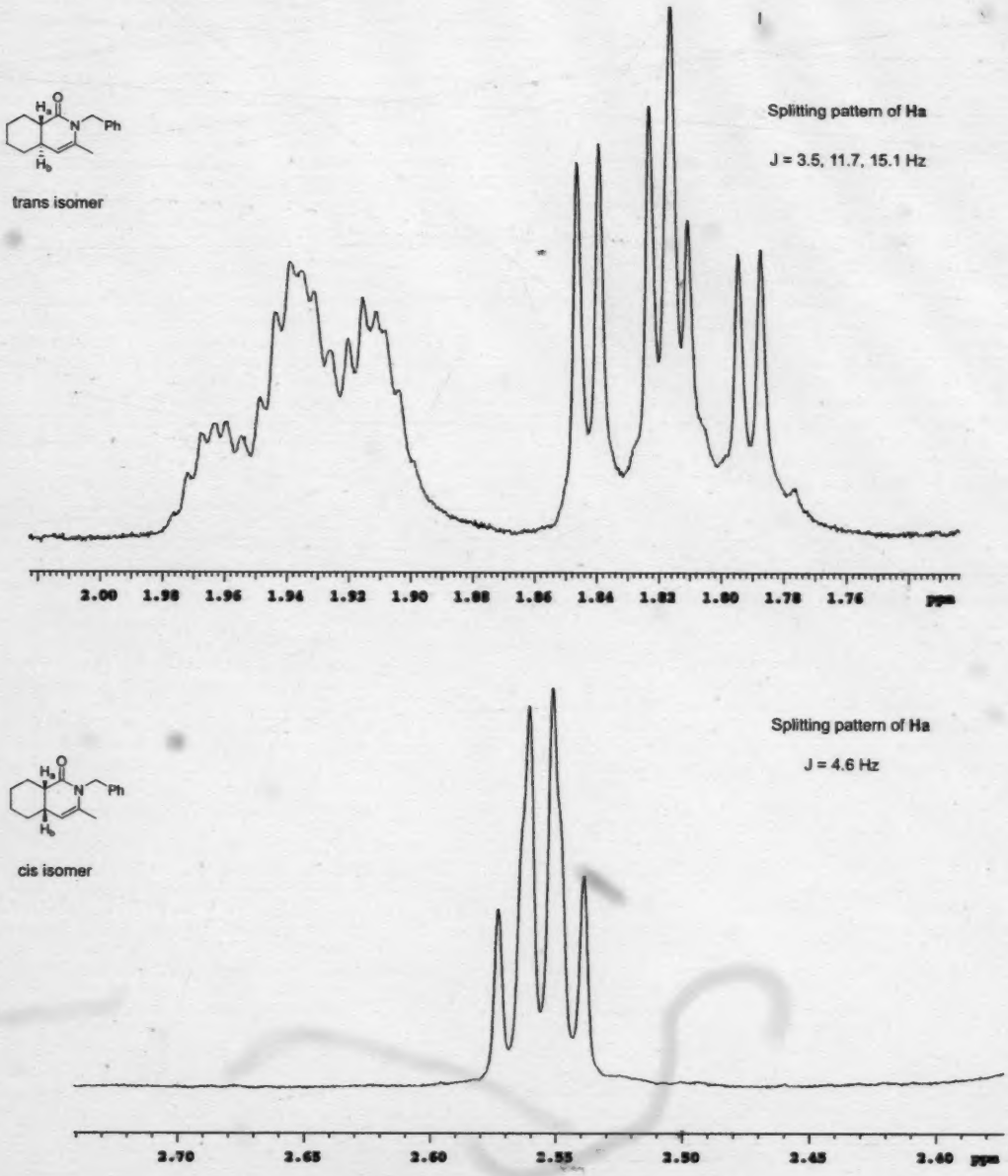
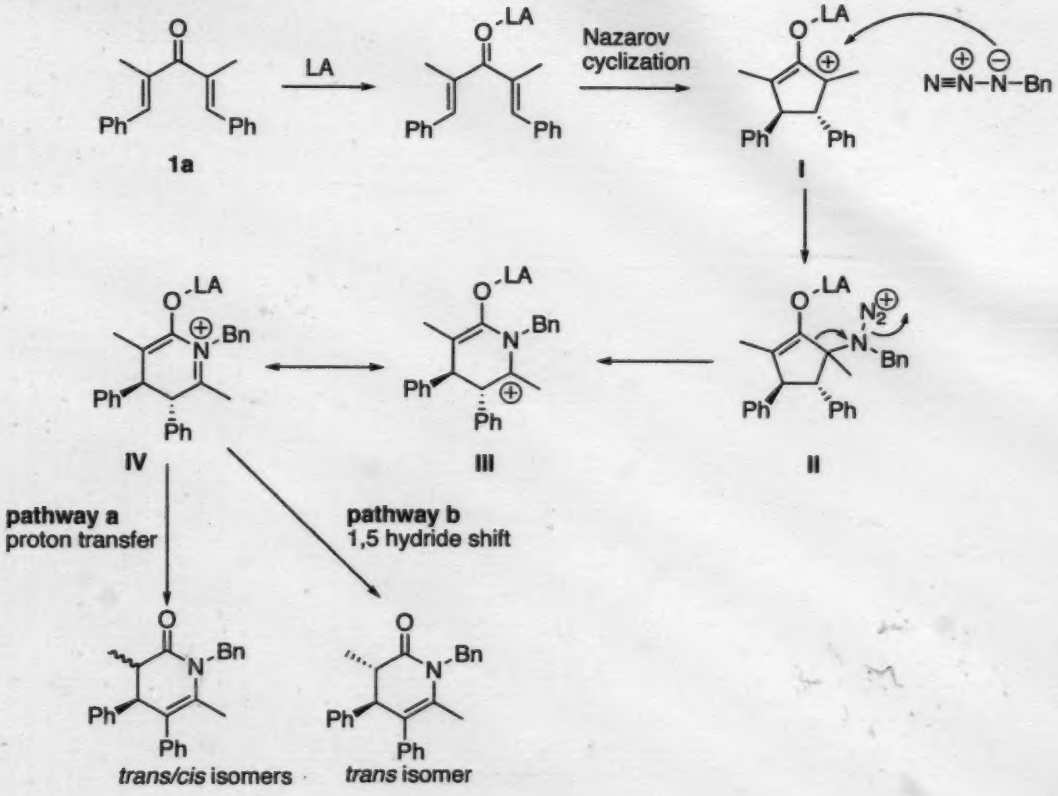

trans isomer
Splitting pattern of Ha
J = 3.5, 11.7, 15.1 Hz
2.00 1.98 1.96 1.94 1.92 1.90 1.88 1.86 1.84 1.82 1.80 1.78 1.76 ppm
cis isomer
Splitting pattern of Ha
J = 4.6 Hz
2.70 2.65 2.60 2.55 2.50 2.45 2.40 ppm

Figure 4. Splitting Patterns of 2d/3d

3.4.3 Mechanistic Proposal

The experimental results suggested (Table 3) a stepwise mechanism for this reaction (Scheme 33). Other possibilities cannot however be ruled out completely. In this proposed mechanism, dibenzylidenepentanone **1a** would first undergo a 4π electron Nazarov cyclization, assisted by $BF_3{\cdot}OEt_2$ to generate an oxyallyl cationic intermediate **I**. The internal azide nitrogen could then act as a nucleophile and attack the carbocation to afford intermediate **II**. This intermediate could then proceed in a C-C bond migration to provide a stable tertiary carbocation **III**, whose resonance form is 1,4-dipole intermediate **IV**. The 1,4-dipole intermediate **IV** could then proceed in one of two pathways. In pathway **a**, intermediate **IV** would lose a β proton next to the iminium ion, followed by protonation of the boron enolate to give a mixture of *trans/cis* isomers. In pathway **b**, a [1,5]-hydride could occur to give only the *trans* isomer.



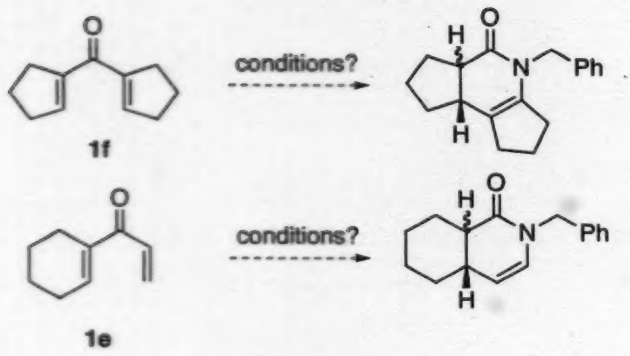
Scheme 33

3.5 Conclusion and Future Work

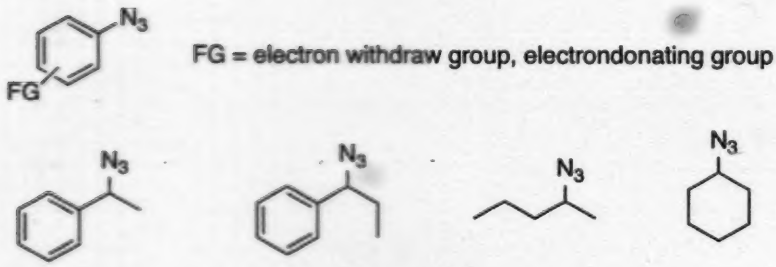
An intermolecular version of the interrupted Nazarov cyclization with alkyl azides was developed. Fully substituted *N*-heterocyclic skeletons can be accessed in a single step from simple dienone and alkyl azide starting materials. The reaction is fast and regioselective. The conditions for this chemistry are relatively mild and the yields are moderate to good. The more stable oxyallyl cation generated after the electrocyclization, the better the observed trapping result. In some cases, complete diastereoselectivity can be obtained as a result of an apparent [1,5] hydride shift pathway. The net result of this reaction is the insertion of the internal azide nitrogen atom into the dienone carbonyl and the neighboring α carbon. This methodology gives an easy access to the preparation of dihydropyridones. Since the starting material is easy to prepare, this methodology has the potential to make a library of N-heterocyclic compounds. Also this methodology could be a useful tool to the synthesis of nitrogen-containing natrual products.

A potential drawback to the methodology is that the dienone can undergo a [3+2] cycloaddition with alkyl azide before the electrocyclization occurs. This suggested that suitable dienone substrates must be reactive enough to complete the Nazarov cyclization before side reaction can complete.

The future work of this project could be the investigation of more dienone substrates (Scheme 34) and organic azides (Scheme 35). The dienones we can investigate are those unsuccessful examples in our previous studies, such as **1e** and **1f**. We can screen different Lewis acids ($TiCl_4$, $FeCl_3$ and $SnCl_4$) and try different reaction temperature to see if the desired trapping products can be obtained. Especially substrate **1f**, the trapping product would be an interesting tricyclic compound. Another way to broaden the reaction scope is to test the different organoazides, such as, aryl azides and secondary alkyl azides. Aryl azides could be electron rich or electron poor and secondary alkyl azides could be linear or cyclic.

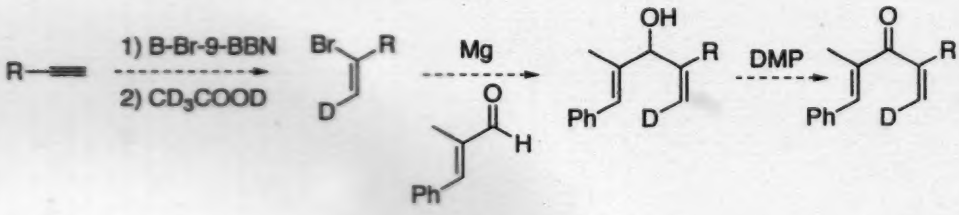


Scheme 34



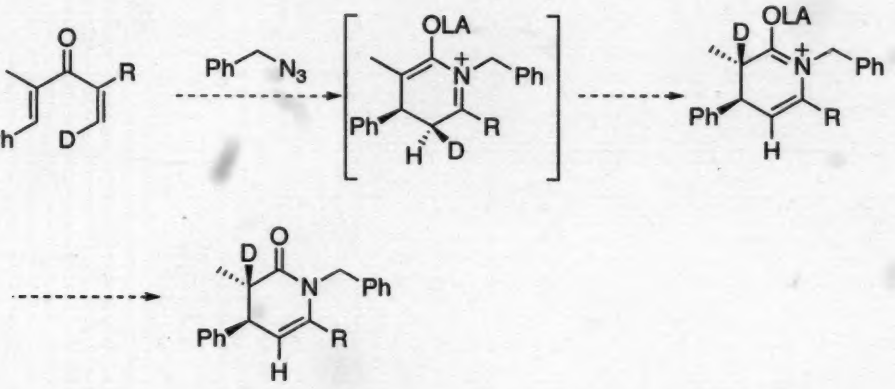
Scheme 35

We can further inverstigate the reaction pathway by doing some deuterium labelling experiments. That would give some ideas of whether the final step of this reaction undergoes the [1,5]-hydride shift or proton transfer. Deuterium labeled dienone substrate can be easily prepared by a sequence of reactions: addition to alkyne by B-Br-9-BBN followed by hydrolysis, addition of Grinard reagent to aldehyde and Dess-Martin oxidation (Scheme 36).



Scheme 36

When deuterium labeled dienone is trapped by benzyl azide, the reaction should generate 1,4 dipole intermediate *in situ*. If [1,5]-hydride shift does involve in the reaction pathway, the deuterium should stereospecifically shift to the α-carbon of the carbonyl group. For the resulting [1,5]-hydride product, the methyl group should be a singlet since there is no neighboring proton. If we couldn't isolate this product, the reaction maybe just undergo a proton transfer process.

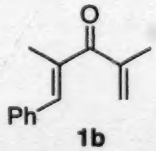


Scheme 37

3.6 Experimental

The copies of selected proton and carbon NMR spectra could be found in Appendix B

Preparation of Dienones

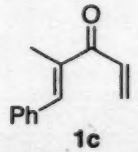


1b

Preparation of 1b. To a solution of 2-bromopropene (1.3 mL, 15 mmol) in THF (10 mL) was added Mg (0.60 g, 25 mmol). The reaction mixture was refluxed for 30 min. The resulting solution was transferred dropwise to a solution of α-methyl-*trans*-cinnamaldehyde (1.50 g, 10 mmol) in THF (10 mL). The reaction mixture was stirred for 2 h at room temperature. Saturated NH_4Cl solution (10 mL) was added to quench the reaction. The resulting mixture was then extracted with CH_2Cl_2 (20 mL)

and the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford the desired dienol as a colorless oil (1.5 g, 80%): R_f 0.54 (5:1 hexanes/EtOAc); IR (thin film) 3375, 1649, 1599, 1491, 1445; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.12 (m, 5H), 6.64 (s, 1H), 5.17-5.12 (m, 1H), 5.02-4.98 (m, 1H), 4.61 (s, 1H), 2.02 (s, 1H), 1.82 (d, 3H, J = 1.3 Hz), 1.73 (d, 3H, J = 0.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 137.9, 137.6, 129.0, 128.1, 126.7, 126.5, 111.6, 81.0, 18.5, 13.5; HRMS (EI) calcd for $C_{13}H_{16}O$ 188.1201, found: m/z 188.1206.

To a solution of the dienol (500 mg, 2.66 mmol) in dichloromethane (25 mL) was added $BaMnO_4$ (1.4 g, 5.32 mmol). The reaction mixture was stirred for 24 h at room temperature before filtration through celite. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford dienone **1b** (297 mg, 60%) as a colorless oil: R_f 0.73 (5:1 hexanes/EtOAc); IR (thin film) 1643, 1622, 1574, 1491, 1447; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.24 (m, 6H), 5.70 (app pentet, 1H, J = 1.5 Hz), 5.59 (app pentet, 1H, J = 1.0 Hz), 2.14 (d, 3H, J = 1.5 Hz), 2.03 (app t, 3H, J = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 143.9, 140.1, 136.5, 135.9, 129.7, 128.4, 128.3, 123.5, 19.3, 14.2; HRMS (EI) calcd for $C_{13}H_{14}O$ 186.1044, found: m/z 186.1042.

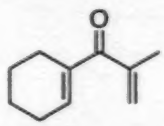


1c

Preparation of 1c. To a solution of α-methyl-*trans*-cinnamaldehyde (1.5 g, 0.011 mmol) in THF (10 mL) was added vinyl magnesium bromide (Aldrich; 1.0 M in THF; 12 mL, 0.012 mmol). The reaction mixture was stirred for 2 h at room temperature. Saturated NH_4Cl solution (10 mL) was then added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (20 mL) and the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified by column

chromatography (silica gel; hexanes/EtOAc 5:1) to afford the desired dienol as a colorless oil (1.48 g, 85%): R_f 0.53 (5:1 hexanes/EtOAc); IR (thin film) 3363 (broad), 1641, 1600, 1492, 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.21 (m, 5H), 6.61 (s, 1H), 5.96 (ddd, 1H, J = 5.8, 10.4, 16.7 Hz), 5.38 (dt, 1H, J = 1.4, 16.7 Hz), 5.24 (dt, 1H, J = 1.4, 10.4 Hz), 4.70 (d, 1H, J = 5.8 Hz), 1.88 (d, 1H, J = 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.8, 137.5, 129.0, 128.1, 126.5, 126.0, 115.7, 78.6, 13.9; HRMS (EI) calcd for $C_{12}H_{14}O$ 173.0966, found: m/z 173.0962; Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.71; H, 8.13.

To a solution of the dienol (70.5 mg, 0.402 mmol) in dichloromethane (5 mL) was added $BaMnO_4$ (412 mg, 1.60 mmol). The reaction mixture was stirred for 24 h at room temperature before filtration through celite. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford dienone **1c** (44.7 mg, 65%) as colorless oil: R_f 0.82 (5:1 hexanes/EtOAc); IR (thin film) 1720, 1657, 1658, 1605, 1491, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.33 (m, 6H), 7.06 (dd, 1H, J = 10.6, 17.0 Hz), 6.33 (dd, 1H, J = 1.8, 17.0 Hz), 5.81 (dd, 1H, J = 1.8, 10.6 Hz), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 139.8, 137.7, 135.8, 132.2, 129.7, 128.6, 128.47, 128.46, 13.5; HRMS (EI) calcd for $C_{12}H_{12}O$ 172.0888, found: m/z 172.0882; Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 84.10; H, 7.37.



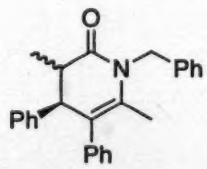
1d

Preparation of 1d. To a solution of 2-bromopropene (1.20 mL, 13.6 mmol) in THF (10 mL) was added Mg (653 mg, 27.2 mmol). The reaction mixture was refluxed for 30 min and the resulting solution was then transferred to a solution of 1-cyclohexene-1-carboxaldehyde (1.0 g, 9.1 mmol) in THF (10 mL). The reaction mixture was stirred for 2 h at room temperature. Saturated NH_4Cl solution (10 mL) was added to quench the reaction. The resulting mixture was further extracted with CH_2Cl_2 (20 mL). Then organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified by

column chromatography (silica gel; hexanes/EtOAc 5:1) to afford the desired dienol as a colorless oil (1.15 g, 83%): R_f 0.60 (5:1 hexanes/EtOAc); IR (thin film) 3372, 1650, 1447; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79-5.75 (m, 1H), 5.05-5.04 (m, 1H), 4.92-4.90 (m, 1H), 4.39-4.38 (m, 1H), 2.12-2.02 (m, 2H), 1.98-1.78 (m, 2H), 1.67-1.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 137.6, 124.0, 110.7, 79.7, 25.1, 23.6, 22.6, 22.5, 18.5; HRMS (EI) calcd for $C_{10}H_{16}O$ 152.1201, found: m/z 152.1201.

To a solution of the dienol (570 mg, 3.75 mmol) in dichloromethane (20 mL) was added $BaMnO_4$ (1.92 g, 7.5 mmol). The reaction mixture was stirred for 24 h at room temperature before filtration through celite. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford dienone **1d** (337 mg, 60%) as a colorless oil: R_f 0.65 (5:1 hexanes/EtOAc); IR (thin film) 1642, 1450, 1435; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68-6.67 (m, 1H), 5.57-5.56 (m, 1H), 5.42-5.29 (m, 1H), 2.29-2.21 (m, 4H), 1.94-1.93 (m, 3H), 1.70-1.61 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 143.7, 141.6, 138.1, 122.3, 25.9, 23.7, 22.0, 21.7, 19.2; HRMS (EI) calcd for $C_{10}H_{14}O$ 150.1044, found: m/z 150.1044.

Trapping of Dienones



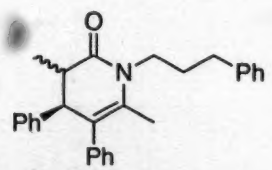
2a/3a

Trapping of 1a with Benzyl Azide 8. To a solution of dienone (100 mg, 0.38 mmol) and benzyl azide **8**, (101 mg, 0.76 mmol) in dichloromethane (5 mL) was added BF_3•OEt_2 (53 μL, 0.42 mmol) in –78°C (dry ice/acetone bath). The reaction mixture was stirred for 10 min. Saturated $NaHCO_3$ solution (2 mL) was added to quench the reaction and the resulting mixture was extracted with CH_2Cl_2 (20 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was then

evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford the *trans* isomer **2a** (76.7 mg, 55% yield) and *cis* isomer **3a** (37.6 mg, 27% yield) as colorless oils.

2a: R_f 0.36 (5:1 hexanes/EtOAc); IR (microscope) 1667, 1599, 1494, 1453 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.36-6.84 (m, 15H), 5.08 (d, 1H, J_{AB} = 15.4 Hz), 4.58 (d, 1H, J_{AB} = 15.4 Hz), 3.34 (d, 1H, J = 7.0 Hz), 2.94 (app pentet, 1H, J = 7.0 Hz), 1.67 (d, 3H, J = 0.7 Hz), 1.19 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 171.6, 141.5, 139.3, 138.1, 132.8, 129.5, 129.2, 128.7, 128.6, 128.5, 128.4, 127.4, 127.2, 126.8, 122.5, 50.7, 45.9, 40.7, 16.8, 13.5; HRMS (EI) calcd for $C_{26}H_{25}ON$ 367.1936, found: m/z 367.1934; Anal. Calcd for $C_{26}H_{25}ON$: C, 84.98; H, 6.86; N, 3.81. Found: C, 84.67; H, 7.03; N, 3.72.

3a: R_f 0.32 (5:1 hexanes/EtOAc); IR (microscope) 1667, 1599, 1494, 1453 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.18-6.91 (m, 15H), 5.16 (d, 1H, J_{AB} = 15.7 Hz), 4.46 (d, 1H, J_{AB}= 15.7 Hz), 3.33 (s, 1H), 3.02 (dq, 1H, J = 2.0, 7.3 Hz), 1.65 (d, 3H, J = 0.5 Hz), 1.37 (d, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 141.0, 140.5, 138.2, 132.1, 129.1, 128.4, 128.3, 128.1, 127.4, 127.3, 127.0, 126.7, 126.6, 118.1, 50.9, 45.2, 43.9, 17.7, 16.7; HRMS (EI) calcd for $C_{26}H_{25}ON$ 367.1936, found: m/z 367.1929.



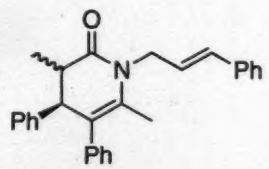
4a/5a

Trapping of 1a with Azide 9. Dienone **1a** was treated with 1-azido-3-phenylpropane **9** following the procedure given above for **2a/3a**. Purification by column chromatography (silica gel; hexanes/EtOAc 5:1) afforded *trans* isomer **4a** (81.0 mg, 54%) and *cis* isomer **5a** (36.0 mg, 24%) as colorless oils.

4a: R_f 0.49 (5:1 hexanes/EtOAc); IR (film microscope) 1668, 1617, 1495, 1452, 1394 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.18 (m, 11H), 7.04-6.98 (m, 4H),

4.01 (ddd, 1H, J = 6.2, 9.8, 14.0 Hz), 3.53 (ddd, 1H, J = 5.6, 10.0, 14.3 Hz), 3.51 (d, 1H, J = 7.0 Hz), 3.14 (app pentet, 1H, J = 7.0 Hz), 2.80-2.65 (m, 2H), 2.12-1.98 (m, 2H), 1.88 (s, 3H), 1.07 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 141.4, 140.9, 137.6, 132.0, 129.2, 128.7, 128.4, 128.3, 128.3, 128.2, 127.0, 126.6, 126.0, 123.0, 50.3, 42.3, 40.3, 33.5, 30.4, 16.5, 12.8; HRMS (EI) calcd for $C_{28}H_{29}ON$ 395.2249, found: m/z 395.2252. Anal. Calcd for $C_{28}H_{29}ON$: C, 82.98; H, 7.60; N, 4.40. Found: C, 82.71; H, 7.63; N, 3.92.

5a: R_f 0.46 (5:1 hexanes/EtOAc); IR (film microscope) 1667, 1599, 1494, 1453, 1394 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.06 (m, 15H), 4.03 (ddd, 1H, J = 6.5, 9.3, 14.1 Hz), 3.45 (ddd, 1H, J = 6.5, 8.8, 14.1 Hz), 3.44 (app s, 1H), 2.83 (dq, 1H, J = 1.7, 7.2 Hz), 2.71-2.59 (m, 2H), 1.96-1.84 (m, 2H), 1.92 (s, 3H), 1.43 (d, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 141.4, 141.3, 140.9, 131.7, 129.2, 128.6, 128.4, 128.3, 128.2, 127.3, 126.8, 126.7, 126.0, 118.5, 51.2, 44.1, 41.6, 33.3, 30.7, 17.6, 16.3; HRMS (EI) calcd for $C_{28}H_{29}ON$ 395.2249, found: m/z 395.2245. Anal. Calcd for $C_{28}H_{29}ON$: C, 82.98; H, 7.60; N, 4.40. Found: C, 82.02; H, 7.61; N, 4.03.



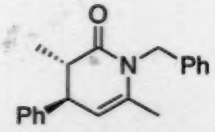
6a/7a

Trapping of 1a with Azide 10. Dienone **1a** was treated with cinnamyl azide **10** following the procedure given above for **2a/3a**. Purification by column chromatography (silica gel; hexanes/EtOAc 5:1) afforded *trans* isomer **6a** (85 mg, 57%) and *cis* isomer **7a** (42 mg, 28%) as colorless oils.

6a: R_f 0.28 (5:1 hexanes/EtOAc); IR (cast film) 1667, 1598, 1492,1431, 1391 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.01 (m, 15H), 6.63 (d, 1H, J = 16.0 Hz), 6.37 (ddd, 1H, J = 5.9, 6.9, 16.0 Hz), 4.83 (ddd, 1H, J = 1.5, 5.9, 15.4 Hz), 4.34 (ddd, 1H, J = 1.2, 6.9, 15.4 Hz), 3.56 (d, 1H, J = 7.1 Hz), 3.22 (app pentet, 1 H, J = 7.0 Hz), 2.04 (d, 3H, J = 0.6 Hz), 1.11 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ

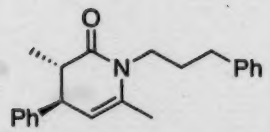
171.5, 140.6, 137.3, 136.6, 132.5, 132.1, 129.1, 128.7, 128.5, 128.3, 128.1, 127.6, 126.9, 126.6, 126.3, 125.3, 123.2, 50.2, 44.3, 40.3, 16.6, 12.8; HRMS (EI) calcd for $C_{28}H_{27}ON$ 393.2092, found: m/z 393.2093.

7a: R_f 0.25 (5:1 hexanes/EtOAc); IR (film microscope) 1668, 1599, 1491, 1449, 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.10 (m, 15H), 6.51 (td, 1H, J = 1.5, 16.0 Hz), 6.22 (ddd, 1H, J = 5.2, 6.9, 16.0 Hz), 4.85 (ddd, 1H, J = 1.6, 5.2, 15.9 Hz), 4.24 (ddd, 1H, J = 1.2, 6.8, 15.9 Hz), 3.52 (app s, 1H), 2.91 (dq, 1H, J = 1.8, 7.2 Hz), 2.06 (d, 3H, J =0.6 Hz), 1.51 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 141.0, 140.6, 136.5, 131.8, 131.7, 129.1, 128.5, 128.4, 128.1, 127.6, 127.3, 126.7, 126.6, 126.3, 125.5, 118.5, 51.1, 44.0, 43.6, 17.5, 16.4; HRMS (EI) calcd for $C_{28}H_{27}ON$ 393.2092, found: m/z 393.2096.



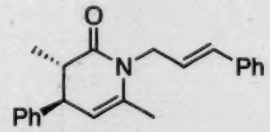
2b

Trapping of 1b with Benzyl Azide 8. To a solution of dienone **1b** (76.0 mg, 0.41 mmol) and benzyl azide[1] **8**, (109.2 mg, 0.82 mmol) in dichloromethane (5 mL) was added $BF_3 \cdot OEt_2$ (116 μL, 0.82 mmol) at –78°C (dry ice/acetone bath). The reaction mixture was stirred for 60 min before saturated $NaHCO_3$ solution (2 mL) was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (20 mL) and the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford only the *trans* product, **2b** (89.5 mg, 75%): R_f 0.56 (5:1 hexanes/EtOAc); IR (film microscope) 1673, 1670, 1604, 1495, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (m, 8H), 7.12-7.04 (m, 2H), 5.22 (dd, 1H, J = 1.0, 5.3 Hz), 4.99 (d, 1H, J_{AB} = 15.7 Hz), 4.89 (d, 1H, J_{AB} = 15.7 Hz) 3.65 (qdd, 1H, J = 1.3, 5.3, 6.0 Hz), 2.97 (app pentet, 1H, J = 7.0 Hz), 2.02 (app t, 3H, J = 1.3 Hz), 1.03 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 139.2, 138.3, 136.0, 128.5, 128.3, 128.2, 127.1, 127.0, 126.7, 108.3, 45.2, 42.4, 40.9, 19.5, 12.1; HRMS (EI) calcd for $C_{20}H_{21}ON$ 291.1623, found: m/z 291.1622.



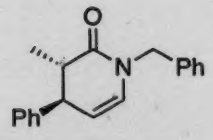
4b

Trapping of 1b with Azide 9. Dienone **1b** was treated with 1-azido-3-phenylpropane **9** following the procedure given above for **2b**. Purification by column chromatography (silica gel; hexanes/EtOAc 5:1) afforded *trans* isomer **4b** (127.6 mg, 80%) as a colorless oil: R_f 0.36 (5:1 hexanes/EtOAc); IR (film microscope) 1665, 1660, 1602, 1551, 1496, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.12 (m, 10H), 5.22 (qd, 1H, J = 1.1, 5.4 Hz), 3.8 (ddd, 1H, J = 5.8, 9.9, 13.9 Hz), 3.58 (ddd, 1H, J = 5.6, 9.9, 14.0 Hz), 3.54 (dd, 1H, J = 5.4, 7.0 Hz), 2.87 (app pentet, 1H, J = 7.0 Hz), 2.70-2.74 (m, 2H), 2.04-1.84 (m, 2H), 1.97 (app s, 3H), 0.98 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 141.3, 139.5, 135.6, 128.3, 128.3, 128.2, 128.1, 126.8, 125.9, 108.5, 42.5, 41.7, 40.7, 33.2, 30.5, 19.2, 12.1; HRMS (EI) calcd for $C_{22}H_{25}ON$ 319.1936, found: m/z 319.1931.



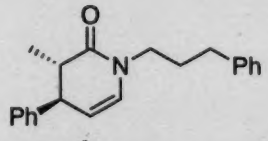
6b

Trapping of 1b with Azide 10. Dienone **1b** was treated with cinnamyl azide **10** following the procedure given above for **2b**. Purification by column chromatography (silica gel; hexanes/EtOAc 6:1) afforded *trans* isomer **6b** (159.7 mg, 72%) as a colorless oil: R_f 0.33 (6:1 hexanes/EtOAc); IR (film microscope) 1674, 1670, 1600, 1495, 1450, 1389 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.12 (m, 10H), 6.56 (d, 1H, J =16.0 Hz), 6.29 (td, 1H, J = 6.1, 16.0 Hz), 5.25 (qd, 1H, J = 1.0, 5.5 Hz), 4.60 (ddd, 1H, J = 1.4, 5.8, 15.8 Hz), 4.37 (ddd, 1H, J = 1.2, 6.2, 15.8 Hz), 3.58 (app t, 1H, J = 5.8 Hz), 2.95 (app pentet, 1H, J = 7.0 Hz), 2.09 (app t, 3H, J = 1.2 Hz), 1.02 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 139.4, 136.6, 135.9, 132.0, 128.6, 128.4, 128.3, 127.7, 126.9, 126.4, 125.4, 108.7, 43.8, 42.7, 40.8, 19.4, 12.3; HRMS (EI) calcd for $C_{22}H_{23}ON$ 317.1779, found: m/z 317.1764.



2c

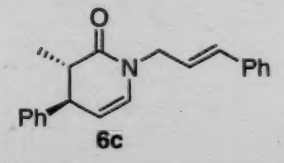
Trapping of 1c with Benzyl Azide 8: To a solution of dienone **1c** (53.0 mg, 0.31 mmol) and benzyl azide **8** (82 mg, 0.62 mmol) in dichloromethane (5 mL) was added BF_3•OEt_2 (43 μL, 0.34 mmol) at room temperature. The reaction mixture was stirred for 15 min before saturated $NaHCO_3$ solution (2 mL) was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (10 mL) and the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford only *trans* product, **2c** (53.2 mg, 62%): R_f 0.62 (5:1 hexanes/EtOAc); IR (film microscope) 1668, 1603, 1494, 1453, 1406 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.18 (m, 8H), 7.04-6.98 (m, 2H), 6.23 (dd, 1H, J = 1.1, 7.7 Hz), 5.35 (dd, 1H, J = 5.2, 7.7 Hz), 4.87 (d, 1H, J_{AB} = 14.7 Hz), 4.62 (d, 1H, J_{AB} = 14.7 Hz), 3.66 (app t, 1H, J = 7.0 Hz), 2.98 (app pentet, 1H, J = 7.1 Hz), 1.01 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 138.9, 137.1, 129.2, 128.7, 128.4, 128.21, 128.20, 127.6, 127.0, 110.1, 49.4, 43.7, 41.0, 12.1; HRMS (EI) calcd for $C_{19}H_{19}ON$ 277.1467, found: m/z 277.1463.



4c

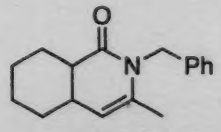
Trapping of 1c with Azide 9: Dienone **1c** was treated with 1-azido-3-phenylpropane **9** following the procedure given above for **2c**. Purification by column chromatography (silica gel; hexanes/EtOAc 5:1) afforded *trans* isomer **4c** (106 mg, 40%) as a colorless oil: R_f 0.38 (5:1 hexanes/EtOAc); IR (film microscope) 1666, 1602, 1495, 1453 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.12 (m, 10H), 6.17 (dd, 1H, J = 1.2, 7.8 Hz), 5.34 (dd, 1H, J = 5.0, 7.8 Hz), 3.66 (dd, 1H, J = 5.0, 7.0 Hz),

3.64 (ddd, 1H, J = 6.4, 8.1, 13.6 Hz), 3.51 (ddd, 1H, J = 6.5, 8.1, 13.8 Hz), 2.88 (app pentet, 1H, J = 7.0 Hz), 2.69 (t, 2H, J = 8.1 Hz), 2.02-1.94 (m, 2H), 0.97 (app s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 141.3, 139.2, 129.6, 128.4, 128.3, 128.2, 128.1, 126.9, 125.9, 109.4, 46.1, 43.5, 40.9, 33.0, 30.0, 11.9; HRMS (EI) calcd for $C_{21}H_{23}ON$ 305.1779, found: m/z 305.1775.



6c

Trapping of 1c with Azide 10. Dienone **1c** was treated with cinnamyl azide **10** following the procedure given above for **2c**. Purification by column chromatography (silica gel; hexanes/EtOAc 5:1) afforded *trans* isomer **6c** (83.3 mg, 43%) as a colorless oil: R_f 0.35 (6:1 hexanes/EtOAc); IR (film microscope) 1666, 1600, 1578, 1494, 1450, 1405, 1386 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.10 (m, 10H), 6.60 (td, 1H, J = 1.3, 15.8 Hz), 6.28-6.20 (m, 2H), 5.38 (dd, 1H, J = 5.0, 7.7 Hz), 4.36 (ddd, 1H, J = 1.3, 6.4, 15.1 Hz), 4.29 (ddd, 1H, J = 1.3, 6.4, 15.1 Hz), 3.68 (app t, 1H, J = 7.1 Hz), 2.96 (app pentet, 1H, J = 7.1 Hz), 1.00 (d, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 139.1, 136.4, 133.3, 129.1, 128.6, 128.5, 128.2, 127.8, 127.0, 126.5, 124.3, 110.1, 47.8, 43.7, 41.0, 12.1; HRMS (EI) calcd for $C_{21}H_{21}ON$ 303.1623, found: m/z 303.1618.



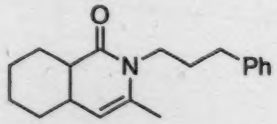
2d/3d

Trapping of 1d with Benzyl Azide 8. To a solution of dienone **1d** (100 mg, 0.67 mmol) and benzyl azide **8** (178 mg, 1.34 mmol) in dichloromethane (5 mL) was added BF_3•OEt_2 (190 μL, 1.34 mmol) at 0 °C (ice-water bath). The reaction mixture was stirred for 60 min before saturated $NaHCO_3$ solution (2 mL) was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (20 mL) and the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent

was evaporated under reduced pressure and the residue purified by column chromatography (silica gel; hexanes/EtOAc 5:1) to afford the *trans* isomer **2d** (90.5 mg, 53%) and the *cis* isomer **3d** (46.1 mg, 27%) as colorless oils.

2d: R_f 0.55 (5:1 hexanes/EtOAc); IR (film microscope) 1675, 1664, 1605, 1496, 1446 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.32-7.10 (m, 5H), 5.18 (d, 1H, J_{AB} = 16.3 Hz), 4.94 (app s, 1H), 4.58 (d, 1H, J_{AB} = 16.3 Hz), 2.25-2.18 (m, 1H), 2.16-2.02 (m, 2H), 1.92-1.82 (m, 2H), 1.82 (app t, 3H, J = 1.4 Hz), 1.80-1.74 (m, 1H), 1.38-1.18 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.3, 139.6, 136.2, 129.7, 128.0, 127.2, 114.1, 46.2, 45.7, 37.0, 33.2, 27.5, 26.7, 26.6, 19.1; HRMS (EI) calcd for $C_{17}H_{21}ON$ 255.1623, found: m/z 255.1628.

3d: R_f 0.54 (5:1 hexanes/EtOAc); IR (film microscope) 1674, 1670, 1605, 1496, 1446 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.16 (m, 5H), 4.93 (d, 1H, J = 16.0 Hz), 4.88 (d, 1H, J = 4.2 Hz), 4.84 (d, 1H, J = 16.0 Hz), 2.64-2.61 (m, 1H), 2.56-2.48 (m, 1H), 2.16-2.02 (m, 1H), 1.85 (app t, 3H, J = 1.6 Hz), 1.60-1.49 (m, 4H), 1.48-1.36 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 138.7, 134.9, 128.6, 126.8, 126.4, 109.7, 44.8, 42.3, 32.3, 28.7, 24.6, 23.8, 23.6, 19.4; HRMS (EI) calcd for $C_{17}H_{21}ON$ 255.1623, found: m/z 255.1629.



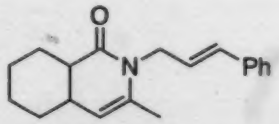
4d/5d

Trapping of 1d with Azide 9: Dienone **1d** was treated with 1-azido-3-phenylpropane **9** following the procedure given above for **2d/3d**. Purification by column chromatography (silica gel; hexanes/EtOAc 5:1) afforded *trans* isomer **4d** (138 mg, 53%) and *cis* isomer **5d** (46 mg, 17%) as colorless oils.

4d: R_f 0.57 (3:1 hexanes/EtOAc); IR (microscope) 1671, 1616, 1496, 1447, 1389; ^1H NMR (500 MHz, C_6D_6) δ 7.16-6.98 (m, 5H), 4.52 (app s, 1H), 3.98-3.92 (m, 1H), 3.11 (ddd, 1H, J = 5.6, 8.9, 14.0 Hz), 2.52-2.40 (m, 3H), 1.90-1.81 (m, 1H), 1.81-1.62 (m, 4H), 1.60-1.48 (m, 2H), 1.45 (dd, 3H, J = 1.4, 2.5 Hz), 1.38-1.35 (m, 1H), 1.16-

0.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 141.6, 134.4, 128.33, 128.29, 125.9, 112.5, 45.0, 41.3, 35.6, 33.2, 32.1, 30.8, 26.3, 25.7, 25.5, 18.9; HRMS (EI) calcd for $C_{19}H_{25}ON$ 283.1936, found: m/z 283.1934.

5d: R_f 0.53 (3:1 hexanes/EtOAc); IR (microscope) 1672, 1670, 1496, 1446, 1392 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.18-6.98 (m, 5H), 4.61 (d, 1H, J = 5.0 Hz), 3.74 (br s, 1H), 3.32 (br s, 1H), 2.50-2.41 (m, 3H), 2.37 (br s, 1H), 2.04 (br s, 1H), 1.82-1.68 (m, 2H), 1.68-1.58 (m, 1H), 1.51-1.46 (m, 1H), 1.43 (app t, 3H, J = 1.3 Hz), 1.39-1.29 (m, 3H), 1.27-1.19 (m, 1H), 1.15-1.08 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.6, 142.0, 135.0, 128.7, 128.6, 126.2, 109.4, 42.0, 41.3, 33.5, 33.2, 31.4, 29.1, 25.3, 25.1, 23.6, 19.1; HRMS (EI) calcd for $C_{19}H_{25}ON$ 283.1936, found: m/z 283.1933.



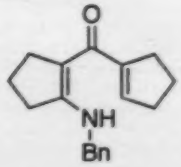
6d/7d

Trapping of 1d with Azide 10. Dienone **12** was treated with cinnamyl azide **10** following the procedure given above for **2d/3d**. Purification by column chromatography (silica gel; hexanes/EtOAc 4:1) afforded *trans* isomer **6d** (150 mg, 52%) and *cis* isomer **7d** (60 mg, 21%) as colorless oils.

6d: R_f 0.45 (4:1 hexanes/EtOAc); IR (film microscope) 1672, 1494, 1447, 1387 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.38-7.16 (m, 5H), 6.41 (td, 1H, J = 1.5, 15.8 Hz), 6.18 (td, 1H, J = 5.4, 16.0 Hz), 4.94 (app s, 1H), 4.61 (ddd, 1H, J = 1.8, 5.0, 16.8 Hz), 4.20 (ddd, 1H, J = 1.6, 5.6, 16.8 Hz), 2.21-2.16 (m, 1H), 2.09-2.02 (m, 1H), 2.02-1.96 (m, 1H), 1.97 (dd, 3H, J = 1.4, 2.3 Hz), 1.90-1.82 (m, 2H), 1.77-1.72 (m, 1H), 1.31-1.18 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.0, 138.1, 136.1, 132.0, 129.6, 128.6, 127.3, 126.6, 113.8, 46.2, 44.3, 37.1, 33.3, 27.4, 26.7, 26.6, 19.0; HRMS (EI) calcd for $C_{19}H_{23}ON$ 281.1779, found: m/z 281.1776.

7d: R_f 0.43 (4:1 hexanes/EtOAc); IR (film microscope) 1673, 1670, 1495, 1447, 1390 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 6.45 (td, 1H, J = 1.5,

16.0 Hz), 6.18 (td, 1H, J = 5.4, 16.0 Hz), 4.90 (d, 1H, J = 4.2 Hz), 4.42 (dd, 1H, J = 5.4, 16.8 Hz), 4.37 (dd, 1H, J = 5.4, 16.8 Hz), 2.61-2.56 (m, 1H), 2.50-2.42 (m, 1H), 2.10-1.98 (m, 1H), 1.96 (t, 3H, J = 1.5 Hz), 1.60-1.42 (m, 4H), 1.42-1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 136.7, 134.7, 130.7, 128.4, 127.4, 126.2, 126.0, 109.6, 43.1, 42.1, 32.2, 28.6, 24.5, 23.8, 23.4, 19.1; HRMS (EI) calcd for $C_{19}H_{23}ON$ 281.1779, found: m/z 281.1775.



11

Trapping of 1f with Azide 8. To a solution of dienone **1f** (50 mg, 0.31 mmol) and azide **8** (82 mg, 0.62 mmol) in dichloromethane (5 mL) was added $BF_3{\cdot}OEt_2$ (43 μL, 0.34 mmol) at -78°C. There was no reaction observed (TLC) after 30 min. The reaction mixture was therefore warmed to 0°C and stirred for another 30 mins. Saturated $NaHCO_3$ solution (5 mL) was added to quench the reaction. The resulting mixture was further extracted with CH_2Cl_2 (10 mL), and the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford **11** (54 mg, 65% yield) as a colorless oil: R_f 0.34 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.6 (br s, 1H), 7.38-7.20 (m, 5H), 6.32-6.30 (m, 1H), 4.46 (d, 2H, J = 6.4 Hz), 2.76 (t, 2H, J = 7.0 Hz), 2.70-2.65 (m, 2H), 2.58 (t, 2H, J = 7.7 Hz), 2.55-2.50 (m, 2H), 1.90-1.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 169.0, 146.7, 138.3, 136.1, 128.7, 127.4, 127.0, 105.2, 48.6, 34.1, 32.9, 31.6, 31.5, 22.5, 22.2.

3.7 Reference and Notes

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CHAPTER 4

ATTEMPTED GENERATION OF DIALKOXYCARBENES FROM THIONOCARBONATES, AND THEIR ATTEMPTED TRAPPING WITH ELECTRON-DEFICIENT 1,3-DIENES

4.1 Introduction

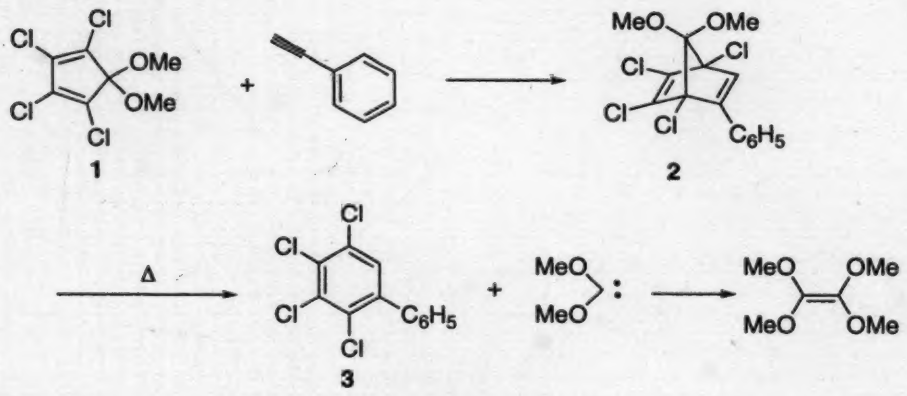
There are many natural products that possess five-membered carbo- and heterocyclic substructures. One could imagine that a [4+1]-cycloaddition between a diene and a carbene would provide quick access to these ring skeletons (Scheme 1). To date, this reaction has had limited success because carbenes and carbenoids prefer to give cyclopropanation products with 1,3-dienes.[1-3] Dimethoxycarbene has attracted considerable attention in recent years due to the resonance stabilization of the singlet state by donor substituents.[4-6] An introduction to [4+1]-cycloaddition reactions involving dimethoxycarbene, a typical nucleophilic carbene,[7] is provided below.

Scheme 1

4.1.1 Generation of Dimethoxycarbene

Thermolysis of norbornadienone acetals

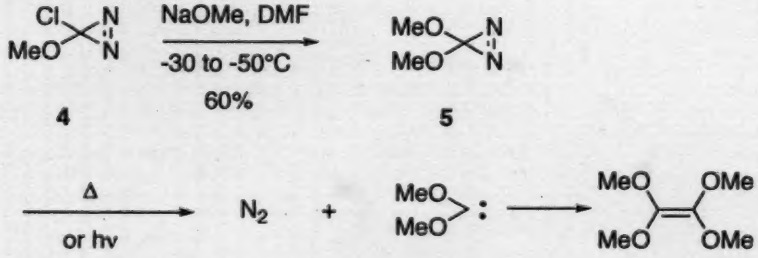
The reactive and nucleophilic dimethoxycarbene has been generated by thermolysis of norbornadienone acetals.[8-10] Diels-Alder addition of commercially available 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, **1**, to phenylacetylene led to cycloadduct **2**. Upon heating to 100-150°C, the substrate **2** decomposed with formation of **3** and dimethoxycarbene, which then dimerized to provide tetramethoxyethylene (Scheme 2).



Scheme 2

Photolysis/thermolysis of dimethoxydiazirines

Dimethoxycarbene has also been generated by photolysis or thermolysis of dimethoxydiazirines.[7,11,12] Treatment of 3-chloro-3-methoxydiazirine,[13] **4**, with excess NaOMe in DMF at -30 to -50°C resulted in the formation of dimethoxydiazirine, **5**, in 60% yield. Upon heating or irradiation, compound **5** lost nitrogen to generate dimethoxycarbene, which then dimerized to give tetramethoxyethylene (Scheme 3).

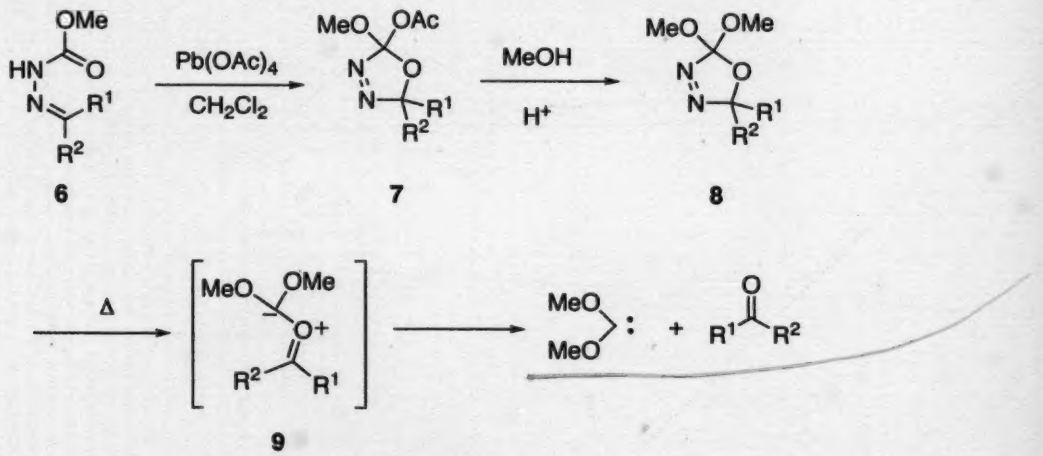


Scheme 3

Thermolysis of oxadiazolines

Recently, Warkentin and co-workers have reported the thermolysis of 2,2-dialkoxy-Δ^3-1,3,4-oxadiazolines as a mild alternative for the generation of dimethoxycarbene (Scheme 4).[14-16] Oxidative cyclization of ketone hydrazones **6**

with lead tetraacetate resulted in the acetoxy substrate **7**. Acid catalyzed displacement of the acetoxy with a methoxy group resulted in oxadiazoline **8**. Upon heating, oxadiazoline **8** extruded nitrogen to afford carbonyl ylide **9**, which then decomposed to generate dimethoxycarbene and the corresponding ketone.



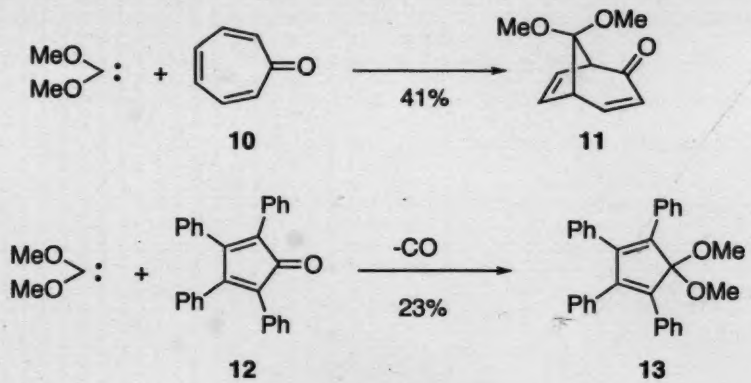
6 **7** **8**

Scheme 4

4.1.2 [4+1]-Cycloaddition of Dimethoxycarbene with 4π Conjugated Systems

Addition of dimethoxycarbene to a diene

Hoffmann and co-workers first reported the generation of dimethoxycarbene by thermolysis of **2** added to tropone **10** and tetracyclone **12** to give the [4+1]-cycloadducts **11** and **13** respectively (Scheme 5).[17] The yield may be lower, but these results indicated a need for further investigation into [4+1]-cycloaddition reactions.



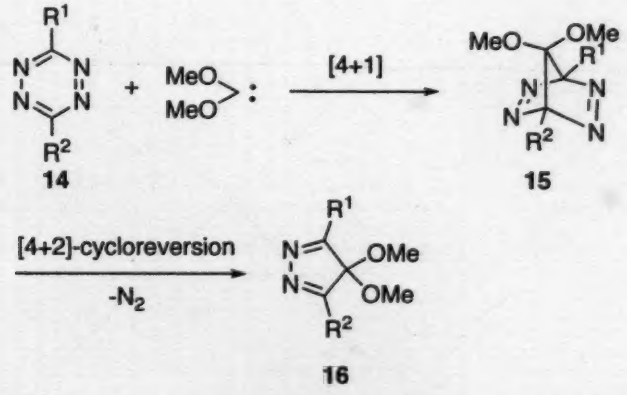
10 **11**

12 **13**

Scheme 5

Addition of dimethoxycarbene to tetrazines

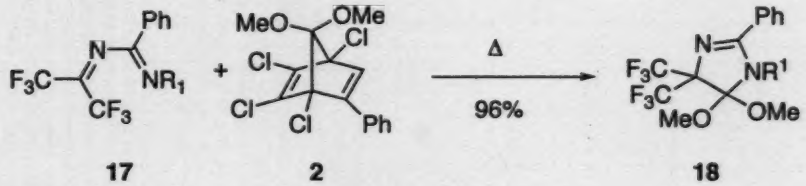
Dimethoxycarbene, generated by thermolysis of compound **2** has also been reported to add into tetrazines.[18] Treatment of **14** with dimethoxycarbene resulted in [4+1]-cycloadduct **15**, which underwent loss of nitrogen gas to give compound **16** (Scheme 6).



Scheme 6

Addition of dimethoxycarbene to 4,4-bis(trifluoromethyl)-1,3-diazobutadiene

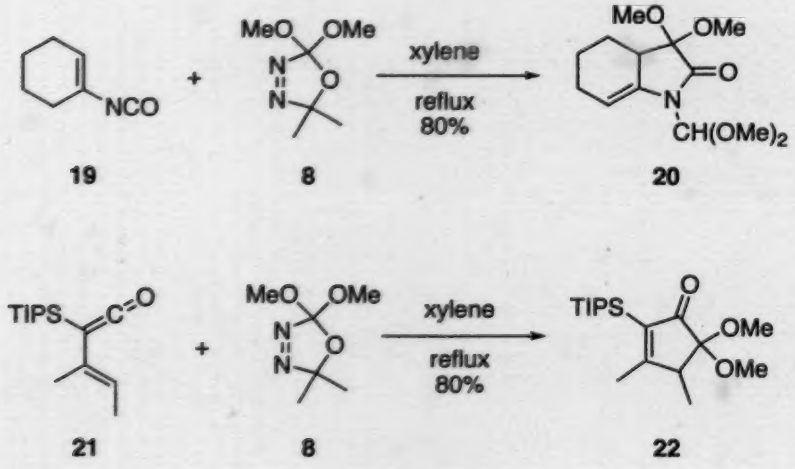
The [4+1]-cycloaddition reaction of 4,4-bis(trifluoromethyl)-1,3-diazobutadiene with dimethoxycarbene has been observed by Burger and co-workers.[19] In this example, dimethoxycarbene was generated by thermolysis of compound **2** and the cycloadduct **18** was obtained in excellent yield (Scheme 7).



Scheme 7

Addition of dimethoxycarbene to vinyl isocyanates and silyl-substituted vinyl ketene

More recently, Rigby and co-workers established that dimethoxycarbene can be added to vinyl isocyanates.[20] Heating 1-isocyanatocyclohexene **19** with excess carbene precursor **8** in xylene provided the functionalized five-membered ring lactam in 80% yield. Two equivalents of carbene were involved in this reaction. In addition, dimethoxycarbene can also react with silyl-substituted vinyl ketene **21** to deliver highly substituted cyclopentenone **22** as the major product in good yield (Scheme 8).[21]



19 **8** **20**

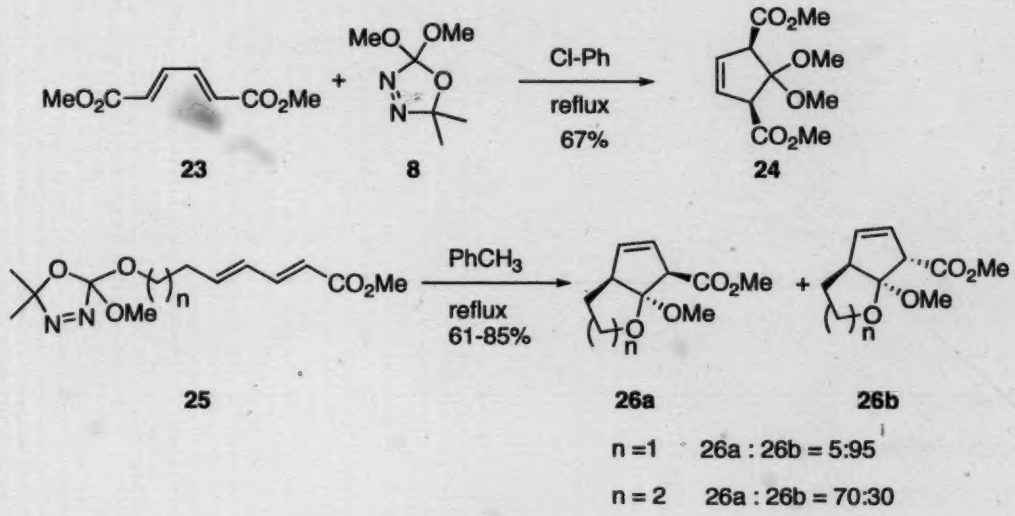
21 **8** **22**

Scheme 8

4.2 Background

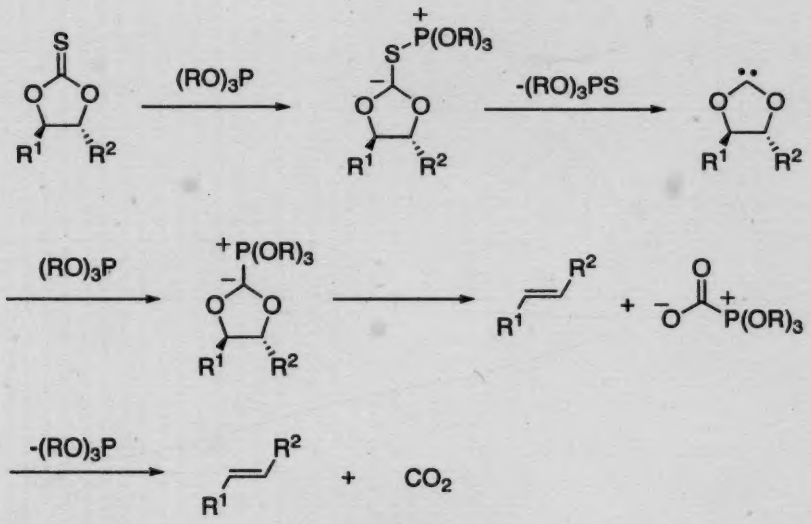
In 2004, Spino and co-workers reported examples of inter- and intramolecular [4+1]-cycloadditions between electron-poor dienes and nucleophilic carbenes (Scheme 9).[22] In the intermolecular version, heating electron-poor diene **23** and carbene precursor **8** afforded cyclopentanone acetal **24** as a single diastereomer. However, intramolecular [4+1]-cycloaddition of **25** gave a mixture of two diastereomers **26a/26b**. The ratio of the two isomers was dependent on ring size. When n was equal to one, a 5:95 mixture of diastereomeric adducts was isolated in 85% yield. When $n = 2$, the two cycloadducts were isolated in a ratio of 70:30 in

61% yield. Based on these results, it is difficult to determine whether this reaction involves a stepwise mechanism or a concerted process.



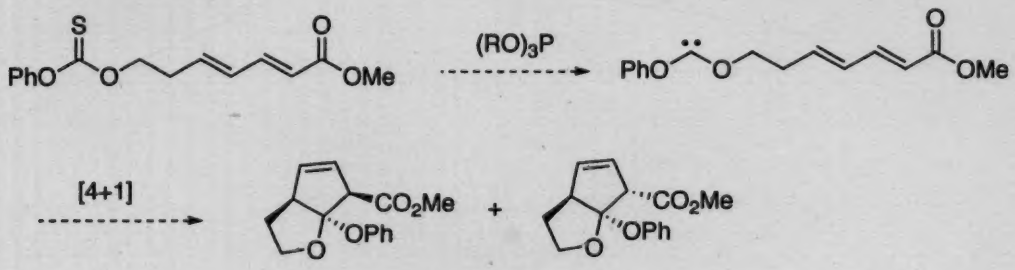
Scheme 9

In the Corey-Winter olefin synthesis,[23] the proposed key intermediate is a dialkoxycarbene (Scheme 10). It is assumed that this reaction proceeds with attack of phosphite on sulfur, followed by decomposition to generate the carbene. This carbene may then react with a second equivalent of phosphite, followed by cycloreversion to yield an alkene and carbon dioxide.



Scheme 10

Inspired by the Corey-Winter reaction, we became interested in the use of thionocarbonates as precursors to nucleophilic carbenes (Scheme 11). The precursor was easy to prepare. The resulting carbene would be used to perform intramolecular [4+1]-cycloadditions to afford products similar to those observed Spino's work. If it were to work, it has potential for asymmetrical induction by using chiral substrates or chiral phosphines.

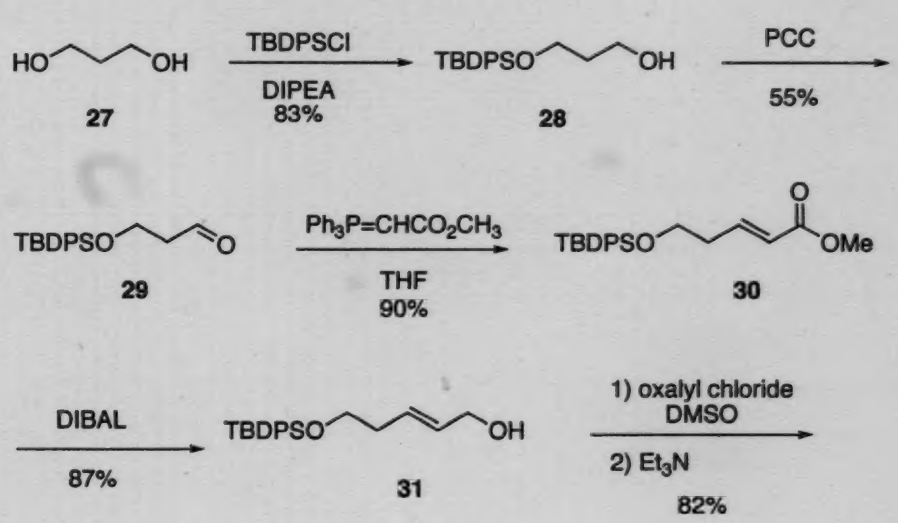


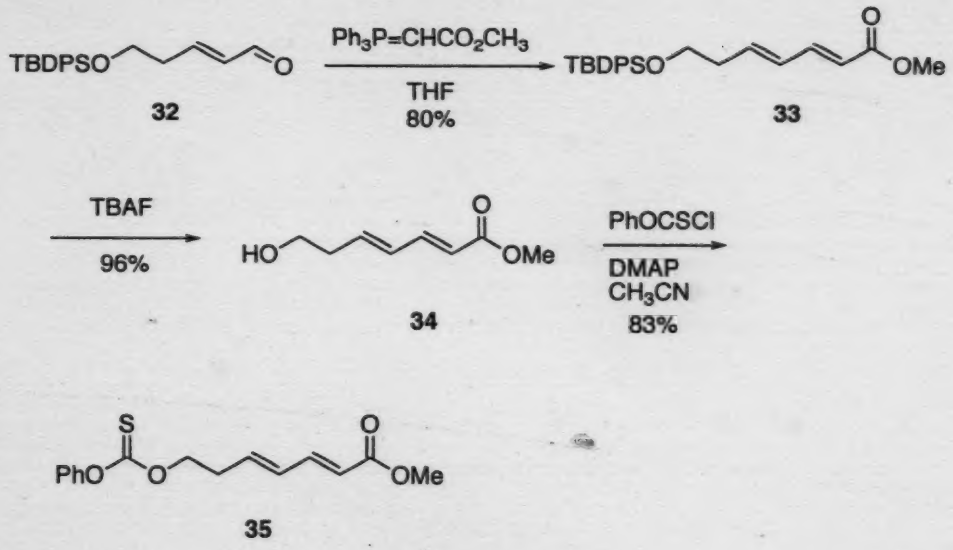
Scheme 11

4.3 Substrate Preparation

We started with the commercially available 1,3 propanediol, **27**. Monoprotection of **27** with a silyl group gave alcohol **28** in 83% yield.[24] Oxidation of

28 with PCC afforded aldehyde **29** in moderate yield. Treatment of aldehyde **29** with methyl (triphenylphosphoranylidene)acetate resulted in the preparation of unsaturated ester **30** in good yield. The unsaturated ester **30** was then reduced to allylic alcohol **31** using DIBAL, followed by Swern oxidation to provide the corresponding enal **32** in 82% yield. Wittig reaction on enal **32** resulted in the diene ester **33** in 80% yield (small amount of *cis* isomer was also obtained). Treatment of **33** with TBAF resulted in desilylation, and subsequent treatment of alcohol **34** with *o*-phenyl chlorothionoformate and DMAP generated the desired thionocarbonate **35** in 83% yield.

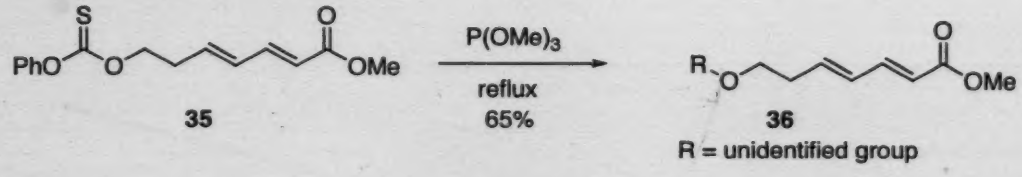




Scheme 12

4.4 Results and Discussion

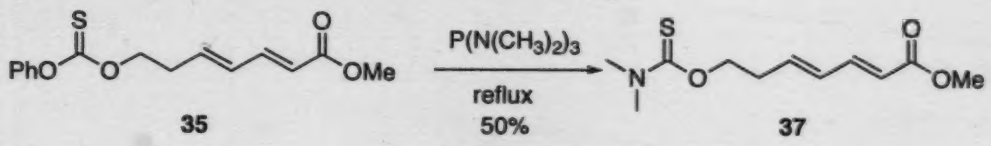
With precursor **35** in hand, we first examined the effect of trimethylphosphite, a reagent commonly used in the Corey-Winter reaction. However, treatment of thionocarbonate **35** in refluxing trimethylphosphite did not afford the desired product. The isolated product could not be identified (Scheme 13). However, the conjugated diene skeleton was not altered by reaction with a pendant carbene. The reason for observing compound **36** is not clear. It appears that thionocarbonate is labile in the presence of trimethylphosphite.



Scheme 13

After the first unsuccessful attempt, we investigated other phosphite and phosphine reagents. When hexamethylphosphorous triamide was used, the isolated

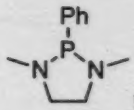
product was tentatively identified as compound **37** (Scheme 37). The results of other unsuccessful reactions are listed in Table 1. The crude proton NMR spectra indicate that the diene was unaffected during the reactions.



35 **37**

Scheme 14

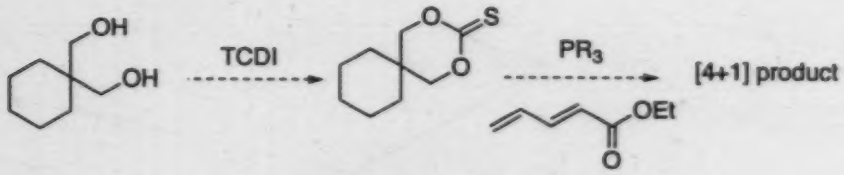
Table 1. Unsuccessful Results of [4+1]-Cycloaddition

Entry	reagent	comments
1	$P(OEt)_3$, reflux	no desired product
2	PBu_3, reflux	no desired product
3	PPh_3, toluene, reflux	no desired product
4	 reflux	no desired product

4.5 Conclusion and Future Work

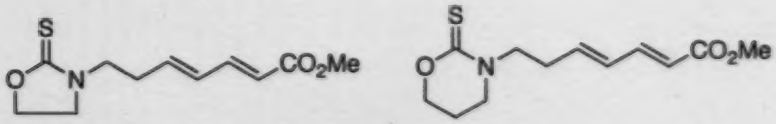
The thionocarbonate **35** was prepared as a nucleophilic carbene precursor; however, treatment of **35** with a variety of phosphites and phosphines did not result in the desired [4+1]-cycloadducts. In all cases, the diene moiety was not affected during the reaction. The only reactive functionality was the thionocarbonate. Given the isolated products **36** and **37**, we cannot establish the reactivity of the thionocarbonate functional group under these conditions. This unsuccessful methodology tells us that either nucleophilic dialkoxycarbene wasn't been generated under these conditions or the carbene prefers to do something else before it can reach the diene moiety. Based on the Corey-Winter reaction in which they proposed a cyclic dialkoxycarbene intermediate, maybe the thiono group that was used to generate nucleophilic carbene needs to be part of a ring.

In the future work, we can consider testing intermolecular [4+1] cycloaddition of carbene and diene moiety to prove that the carbene intermediate is generated in the reaction (Scheme 15). Treatment of commercially available diol with thiocarbonyldiimidazole would result in thiono compound. The resulting thiono compound can react with conjugate diene in the presence of phosphite compound. If the desired [4+1]-cycloadduct can be obtained in this reaction, that could prove that carbene is formed during the reaction. Then we can move to the intramolecular version of [4+1]-cycloadditioon.



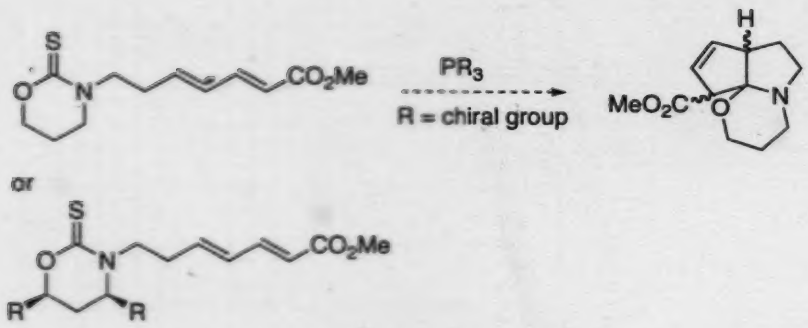
Scheme 15

The following thiono compounds for the intramolecular cycloaddition are worth to try since they have similar skeleton to the Corey-Winter substrates. We have some concern on the five-membered ring substrate since fragment can happen to give O=C=NR. However, it still has a chance to do the [4+1]-cycloaddition if fragmentation is slower than the cycloaddition. In any case the six-membered substrate would avoid this concern.



Scheme 16

If the intramolecular cycloaddition does give the desired cycloadduct, we can further investigate the asymmetrical cycloaddition of dialkoxycarbene and diene moiety. We can use chiral phosphite reagent to induce the [4+1]-cycloaddition to give enantioselective cycloadduct (Scheme 17). Also we can start with chiral thiono compound to obtain the enantioselectivity.

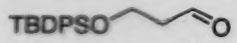


Scheme 17

4.6 Experimental

28

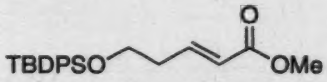
Preparation of 28. To a solution of propanediol (5.0 g, 66 mmol) in dichloromethane (15 mL) was added TBDPSCl (5.6 mL, 22 mmol) and diisopropylethylamine (11.5 mL, 65.8 mmol). The solution was stirred for 5 hours and then diluted with saturated ammonium chloride (40 mL). The resulting organic phase was washed with brine (15 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure and the residue was purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford alcohol **28** (5.7 g, 83%) as a colorless oil: R_f 0.63 (5:1 hexanes/EtOAc); IR (film) 3345, 1589, 1472, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.72 (m, 4H), 7.43-7.39 (m, 6H), 3.92-3.84 (m, 4H), 2.62 (t, 1H, J = 5.4 Hz), 1.85 (quintet, 2H, J = 5.6 Hz), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.4, 129.8, 127.8, 63.0, 61.6, 34.5, 26.9, 19.1; Anal. Calcd for $C_{19}H_{26}O_2Si$: C, 72.56; H, 8.33. Found: C, 72.36; H, 8.53.



29

Preparation of 29. To a solution of alcohol **28** (250 mg, 0.806 mmol) in dichloromethane (5 mL) was added PCC (189 mg, 0.885 mmol) and molecular sieve (4 Å). The solution was stirred for 4 hours before filtration through Celite. The

resulting solution was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure and the residue was purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford aldehyde **29** (137 mg, 55% yield) as a colorless oil: R_f 0.52 (3:1 hexanes/EtOAc); IR (microscope) 2889, 2858, 1728, 1589, 1472, 1428 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (t, 1H, J = 2.2 Hz), 7.68-7.62 (m, 4H), 7.42-7.38 (m, 6H), 4.02 (t, 2H, J = 6.0 Hz), 2.61 (dt, 2H, J = 2.2, 6.0 Hz), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 135.5, 133.3, 129.8, 127.8, 58.3, 46.4, 26.8, 19.1; HRMS (ESI) calcd for $C_{19}H_{24}O_2NaSi$ ($[M•Na]^+$) 335.1438, found 335.1437. Anal. Calcd for $C_{19}H_{24}O_2Si$: C, 73.03; H, 7.74. Found: C, 73.01; H, 7.77.



30

Preparation of 30. To a solution of aldehyde **29** (770 mg, 2.46 mmol) in THF (10 mL) was added methyl (triphenylphosphoranylidene)acetate (904 mg, 2.70 mmol). The solution was heated at reflux for 2 hours before dilution with dichloromethane (20 mL). The resulting solution was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure and the residue purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford ester **30** (815 mg, 90%) as a colorless oil: R_f 0.32 (5:1 hexanes/EtOAc); IR (microscope) 1726, 1660, 1589, 1463, 1428 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.44-7.38 (m, 6H), 6.99 (td, 1H, J = 7.1, 15.8 Hz), 5.88 (td, 1H, J = 1.3, 15.8 Hz), 3.78 (t, 2H, J = 6.4 Hz), 3.74 (s, 3H), 2.45 (app dq, 2H, J = 1.3, 6.4 Hz), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 146.1, 135.6, 133.6, 129.7, 127.7, 122.6, 62.3, 51.4, 35.5, 26.8, 19.2; Anal. Calcd for $C_{22}H_{28}O_3Si$: C, 71.70; H, 7.66. Found: C, 71.60; H, 7.77.

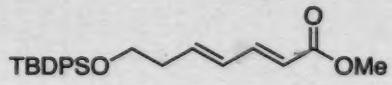
31

Preparation of 31. To a solution of unsaturated ester **30** (3.2 g, 8.7 mmol) in diethyl ether (20 mL) was added diisobutylaluminium hydride (1.0 M in CH_2Cl_2, 19.1 mL, 19.1 mmol) at -78°C. The solution was stirred for 2 hours before dilution with

saturated potassium sodium tartrate (60 mL). The resulting organic phase was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure and the residue purified by column chromatography (silica gel, 4:1 hexanes/EtOAc) to afford alcohol **31** (2.57 g, 87%) as a colorless oil: R_f 0.45 (3:1 hexanes/EtOAc); IR (microscope) 3333, 1670, 1589, 1486, 1472, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74-7.70 (m, 4H), 7.44-7.38 (m, 6H), 5.71-5.68 (m, 2H), 4.09-4.07 (m, 2H), 3.75 (t, 2H, J = 6.6 Hz), 2.37-2.31 (m, 2H), 1.04 (s, 9H) (missing a proton on hydroxy group); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.9, 131.1, 129.6, 129.4, 127.7, 63.7, 63.5, 35.6, 26.9, 19.3; Anal. Calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 74.02; H, 8.42.

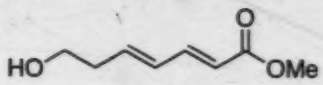
32

Preparation of 32. To a solution of oxalyl chloride (0.79 mL, 9.1 mmol) was added DMSO (1.29 mL, 18.2 mmol) dropwise at -78°C. The solution was stirred for 0.5 hours before dropwise addition of alcohol **31** (2.8 g, 8.2 mmol) in CH_2Cl_2 (10 mL). The solution was stirred for another hour and then triethylamine (3.4 mL, 24.7 mmol) was added dropwise. The resulting mixture was warmed to room temperature and diluted with saturated ammonium chloride (40 mL). The resulting organic phase was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed by reduced pressure and the residue purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford aldehyde **32** (2.28 g, 82%) as a colorless oil: R_f 0.35 (5:1 hexanes/EtOAc); IR (microscope) 2885, 2858, 1694, 1656, 1589, 1472, 1428 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, 1H, J = 7.9 Hz), 7.68-7.66 (m, 4H), 7.48-7.39 (m, 6H), 6.85 (td, 1H, J = 7.0, 15.6 Hz), 6.17 (tdd, 1H, J = 1.4, 7.9, 15.6 Hz), 3.86 (t, 2H, J = 6.1 Hz), 2.56 (app dq, 2H, J = 1.4, 6.1 Hz), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 155.4, 135.6, 134.4, 133.4, 129.8, 127.8, 62.0, 35.9, 26.9, 19.2; Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.32; H, 7.90.



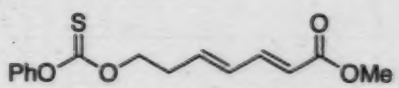
33

Preparation of 33. To a solution of aldehyde **32** (7.74 g, 22.9 mmol) in THF (25 mL) was added methyl (triphenylphosphoranylidene)acetate (8.42 g, 25.2 mmol). The solution was heated at reflux for 2 hours before dilution with dichloromethane (20 mL). The resulting solution was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, 10:1 hexanes/EtOAc) to afford ester **33** (7.22 g, 80%) as a colorless oil: R_f 0.47 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.42-7.36 (m, 6H), 7.25 (dd, 1H, J = 10.5, 15.4 Hz), 6.24-6.09 (m, 2H), 5.80 (d, 1H, J = 15.4 Hz), 3.75 (t, 2H, J = 6.4 Hz), 3.75 (s, 3H), 2.41 (app q, 2H, J = 6.5 Hz), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 145.1, 141.0, 135.5, 133.7, 130.1, 129.6, 127.6, 119.2, 62.8, 51.4, 36.2, 26.8, 19.2



34

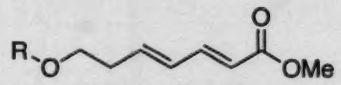
Preparation of 34. To a solution of diene ester **33** (7.13 g, 18.1 mmol) in THF (10 mL) was added TBAF (1.0 M in THF, 19.8 mL, 19.8 mmol). The solution was stirred for 2 hours before dilution with dichloromethane (20 mL). The resulting solution was washed with brine (15 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 3:1 hexanes/EtOAc) to afford alcohol **34** (2.71 g, 96%) as a colorless oil: R_f 0.23 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 1H, J = 10.8, 15.4 Hz), 6.30-6.20 (m, 1H), 6.15-6.07 (m, 1H), 5.81 (d, 1H, J = 15.4 Hz), 3.74-3.68 (m, 2H), 3.70 (s, 3H), 2.43 (app q, 2H, J = 6.4 Hz), 1.93 (t, 1H, J = 5.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 144.7, 140.2, 130.5, 119.6, 61.4, 51.5, 36.2.



35

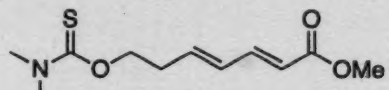
Preparation of 35. To a solution of alcohol **34** (460 mg, 2.95 mmol) in CH_3CN (10 mL) was added O-phenylchlorothionoformate (0.60 mL, 4.4 mmol) and DMAP (1.08

g, 8.85 mmol). The solution was stirred for 2 hours before dilution with dichloromethane (20 mL). The resulting solution was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford product **35** (714 mg, 83%) as a colorless oil: R_f 0.33 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.30-7.24 (m, 2H), 7.10-7.06 (m, 2H), 6.34-6.27 (m, 1H), 6.16-6.10 (m, 1H), 5.87 (d, 1H, J = 15.4 Hz), 4.61 (t, 2H, J = 6.6 Hz), 3.78 (s, 3H), 2.70 (app q, 2H, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 167.4, 153.3, 144.2, 137.7, 131.1, 129.5, 126.6, 121.9, 120.5, 72.4, 51.5, 31.7; Anal. Calcd for $C_{15}H_{16}O_4S$: C, 61.62; H, 5.52; S, 10.97. Found: C, 61.58; H, 5.55; S, 10.56.



36

Preparation of 36. Ester **35** (55 mg, 0.19 mmol) was dissolved in trimethylphosphite (2 mL). The solution was heated at reflux for 2 hours and the crude reaction mixture purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford a product that could not be identified (21 mg, 65%) as a colorless oil: R_f 0.53 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, 1H, J = 10.8, 15.3 Hz), 6.30-6.24 (m, 1H), 6.12-6.06 (m, 1H), 5.84 (d, 1H, J = 15.4 Hz), 4.52 (t, 2H, J = 6.6 Hz), 4.04 (s, 3H), 3.74 (s, 3H), 2.64 (app q, 2H, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 144.3, 137.9, 130.9, 120.3, 71.5, 59.5, 51.5, 31.8.



37

Preparation of 37. Ester **35** (50 mg, 0.17 mmol) was dissolved in tris(dimethylamino)phosphine (2 mL). The solution was heated at reflux for 2 hours and the crude reaction mixture purified by column chromatography (silica gel, 5:1 hexanes/EtOAc) to afford product (21 mg, 50%) as a colorless oil: R_f 0.43 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, 1H, J = 10.8, 15.3 Hz), 6.28-6.22 (m, 1H), 6.12-6.06 (m, 1H), 5.84 (d, 1H, J = 15.4 Hz), 4.56 (t, 2H, J = 6.6 Hz), 3.74 (s, 3H), 3.38 (s, 3H), 3.02 (s, 3H), 2.60 (app q, 2H, J = 6.7 Hz); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 187.9, 167.5, 144.5, 139.1, 130.5, 120.0, 69.6, 51.5, 42.7, 37.7, 32.4; HRMS (EI) calcd for $C_{11}H_{17}O_3NS$ 243.0929, found: m/z 243.0931.

4.7 References and Notes

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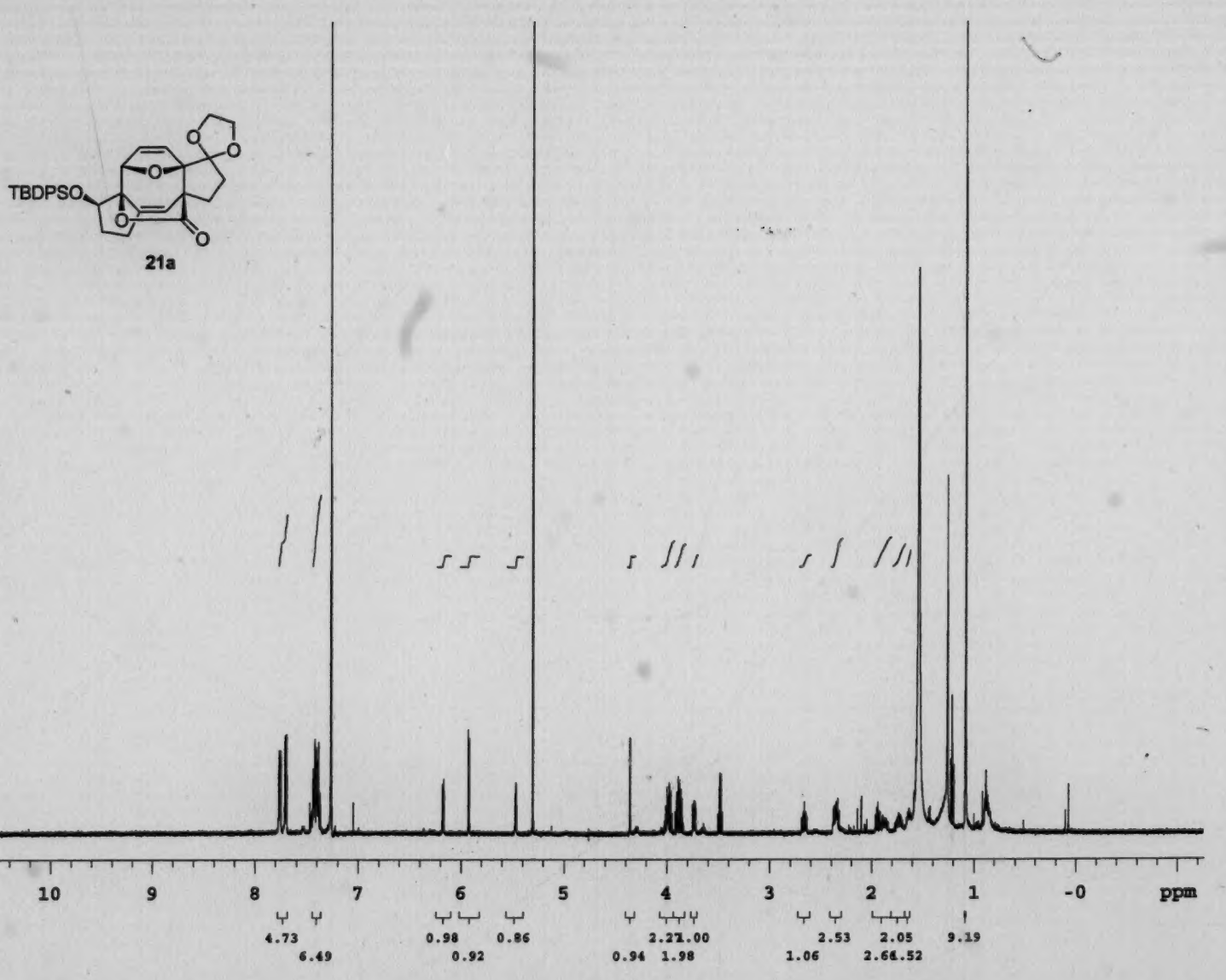
APPENDIX A

CHAPTER 2 NMR SPECTRA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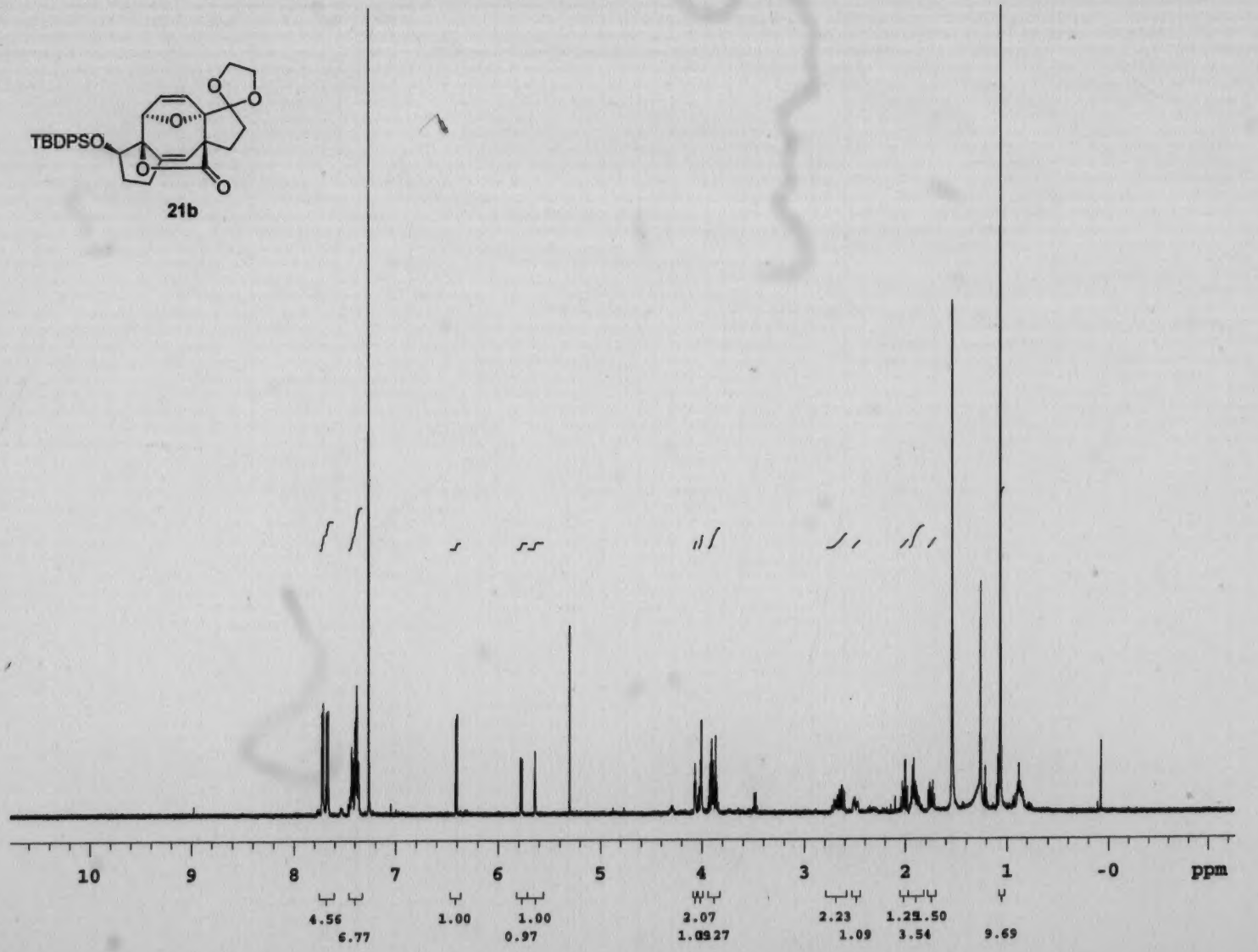
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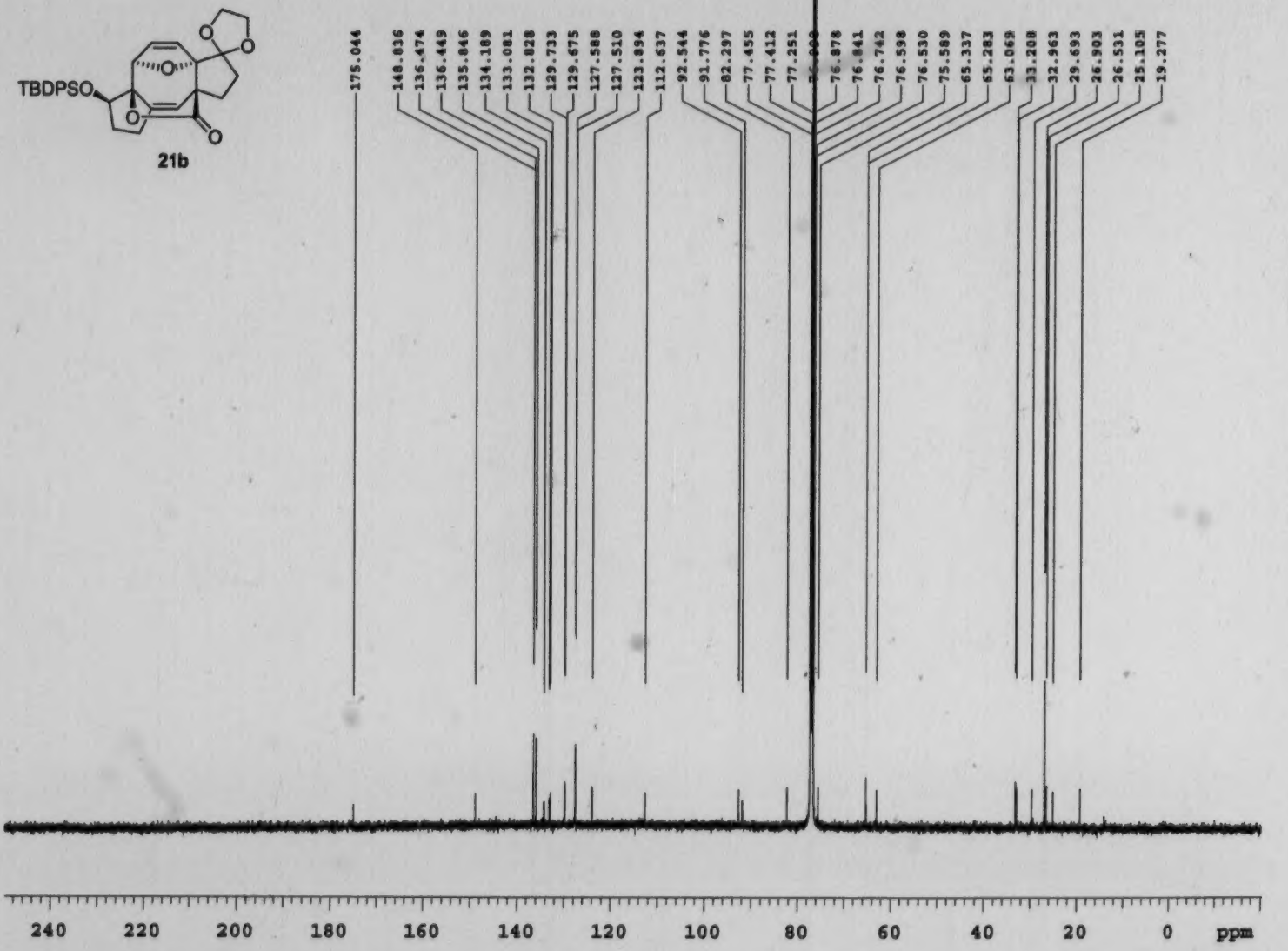
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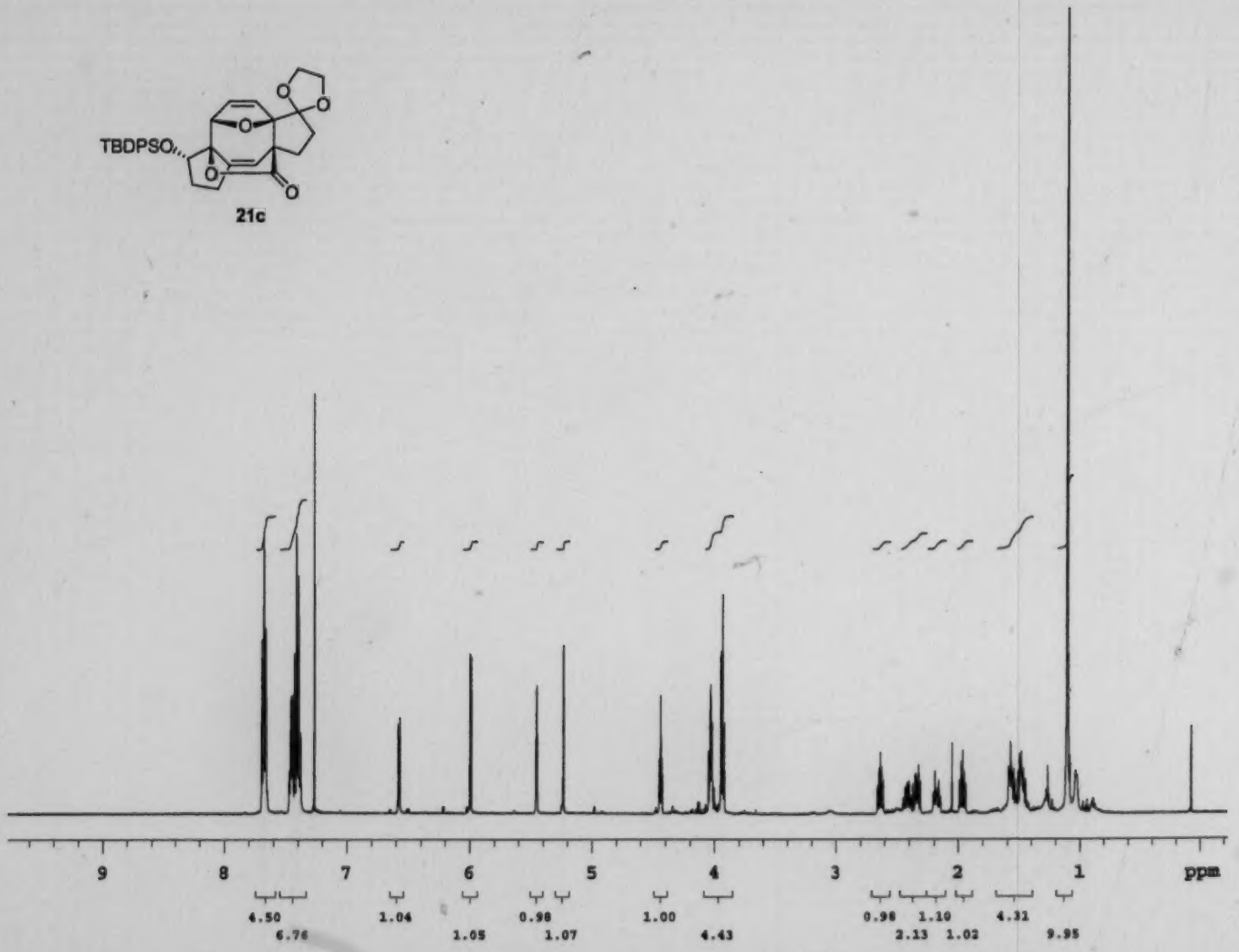
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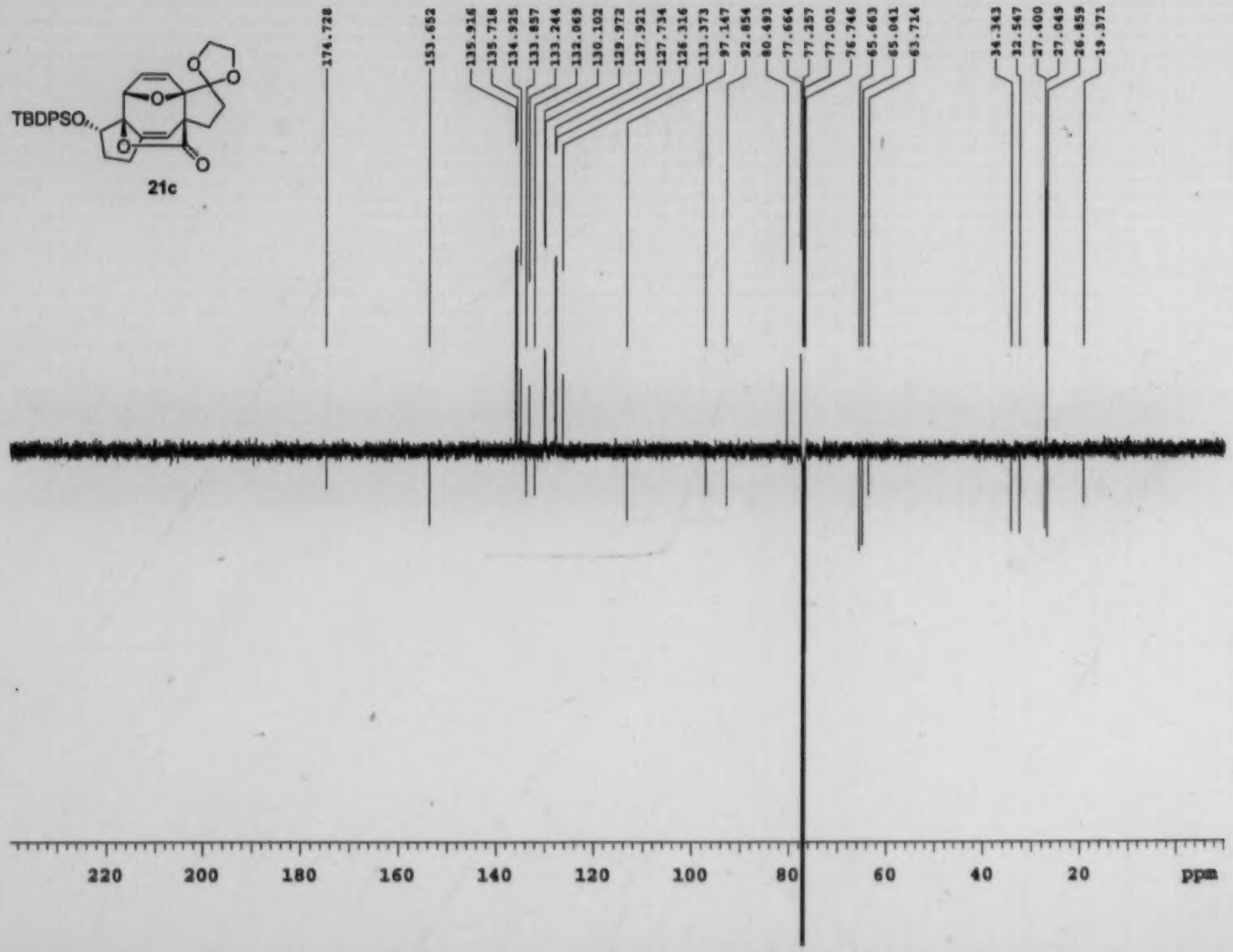
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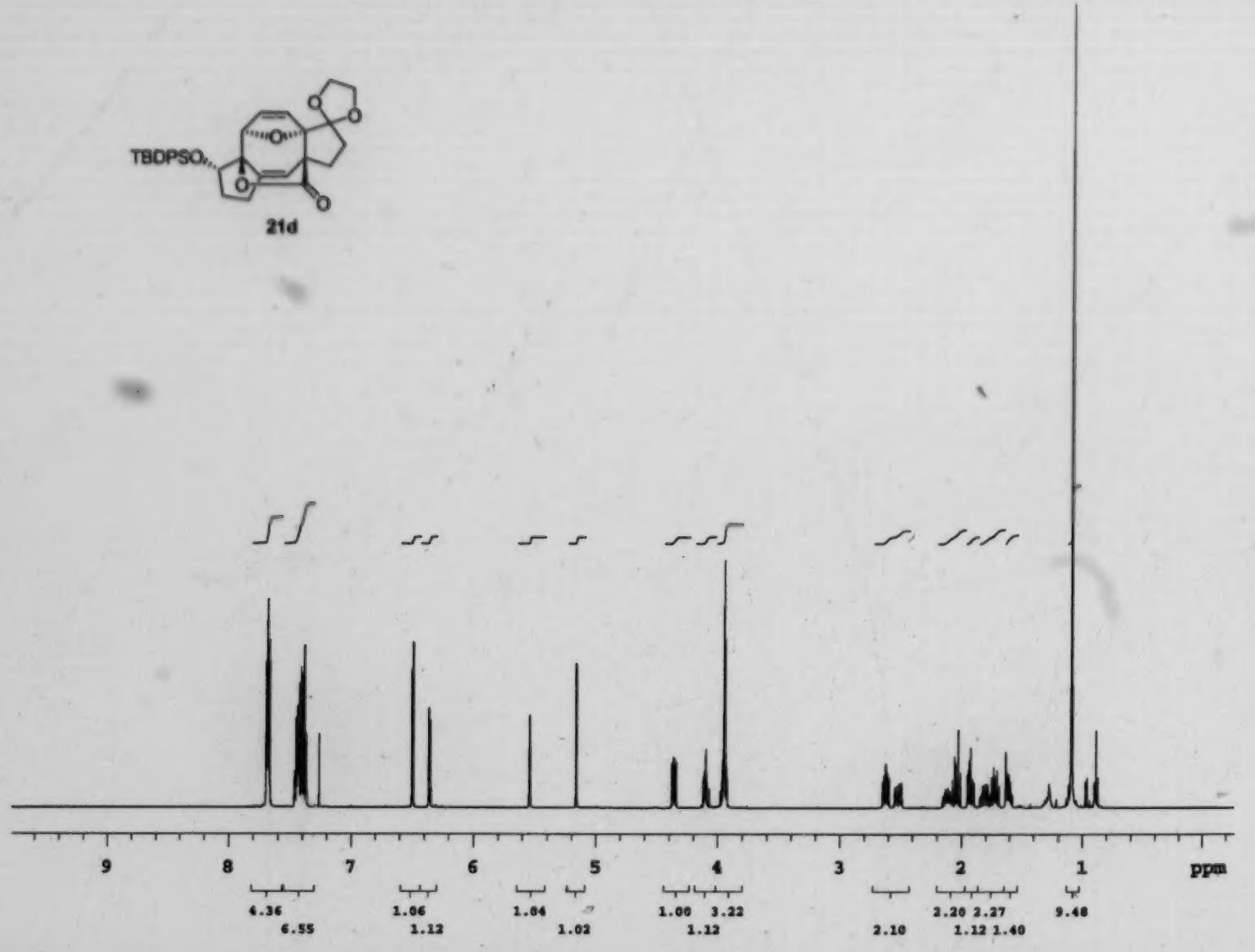
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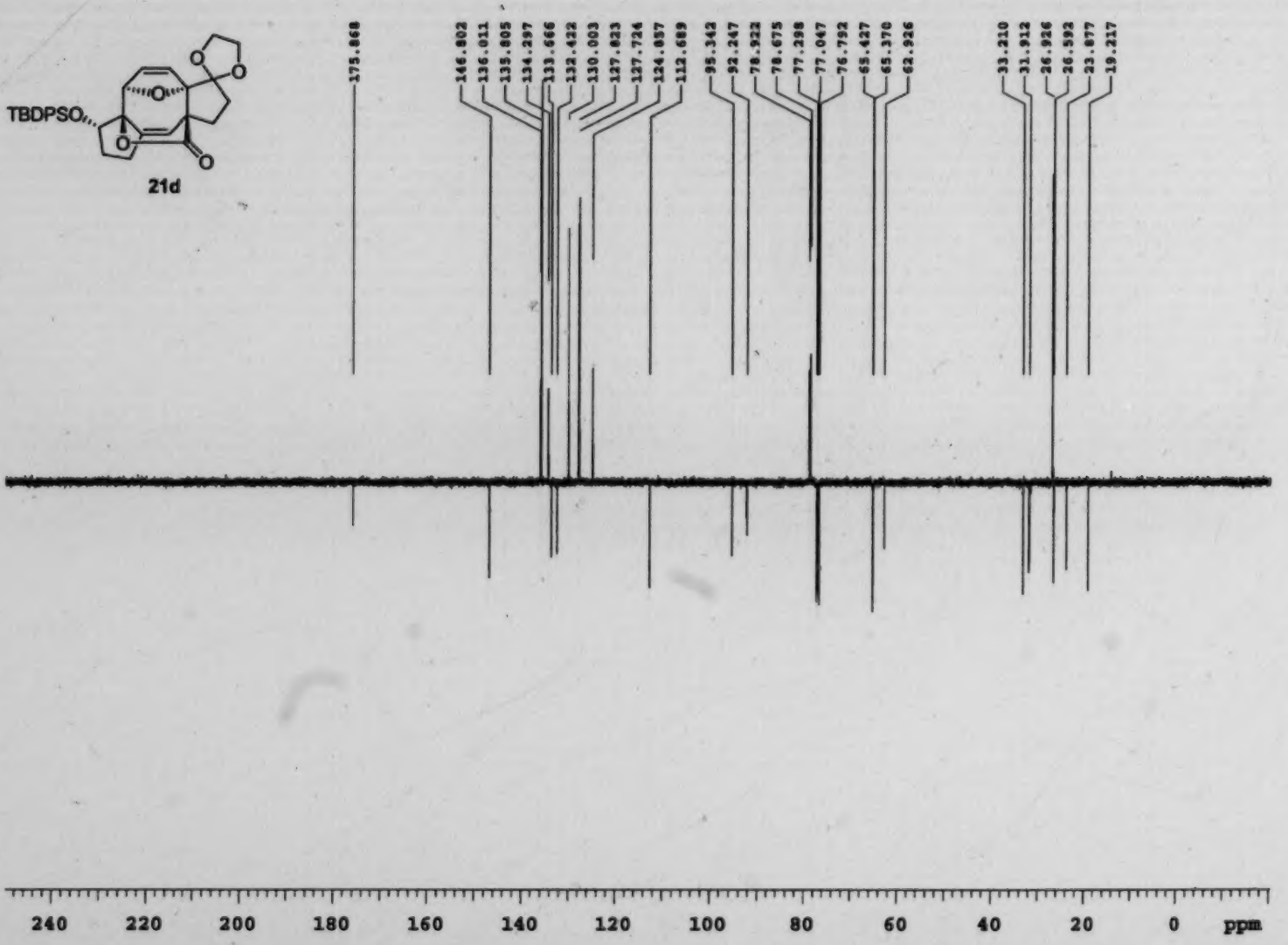
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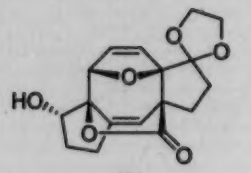
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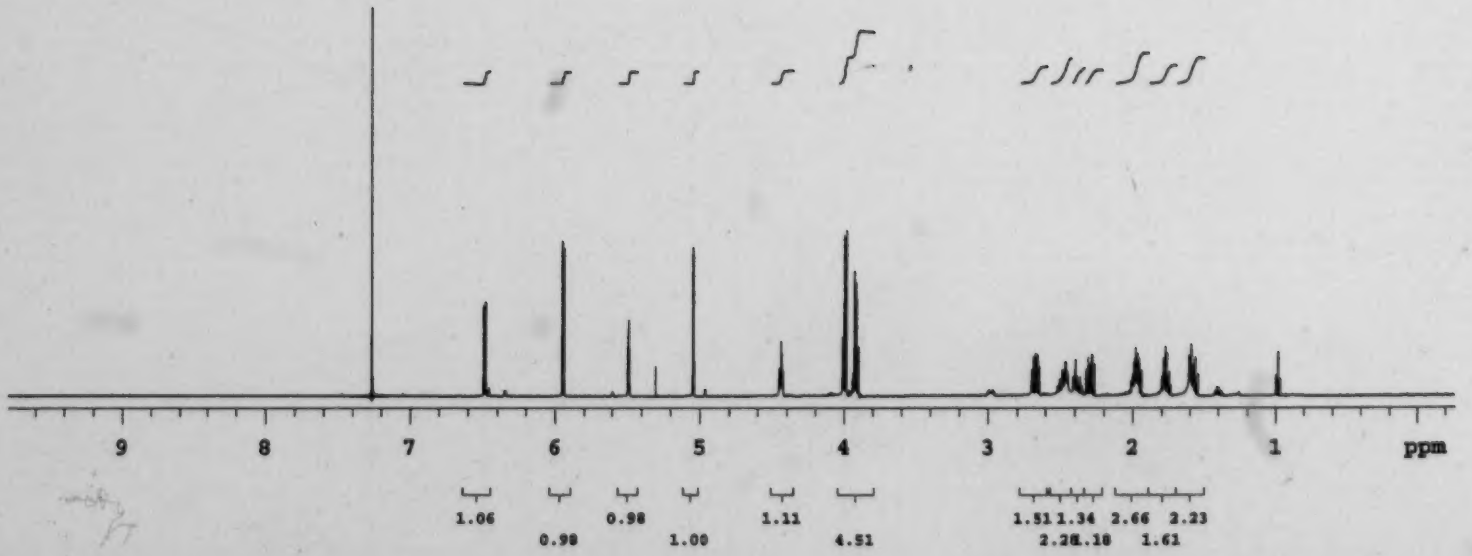
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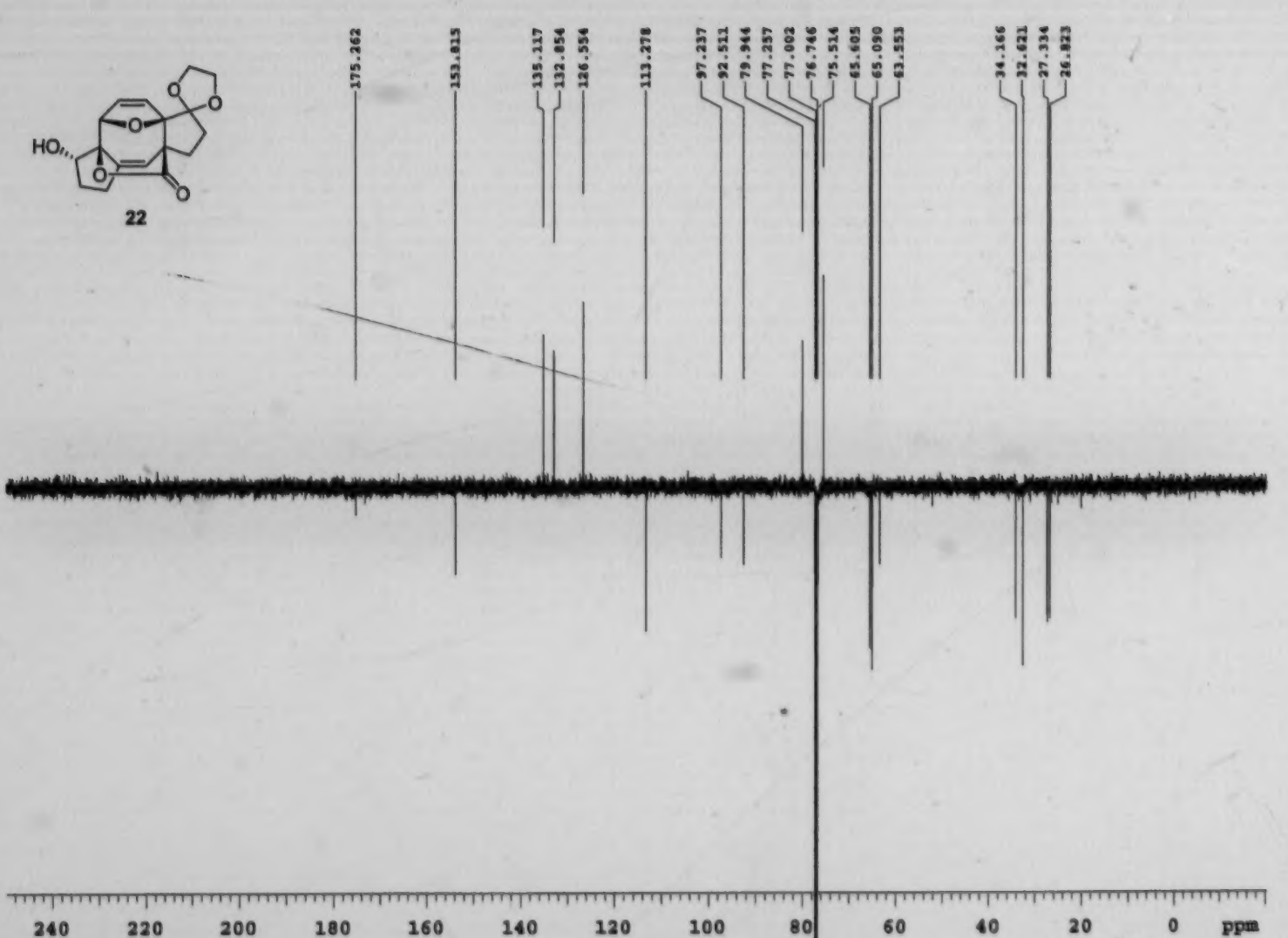
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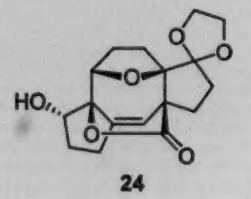
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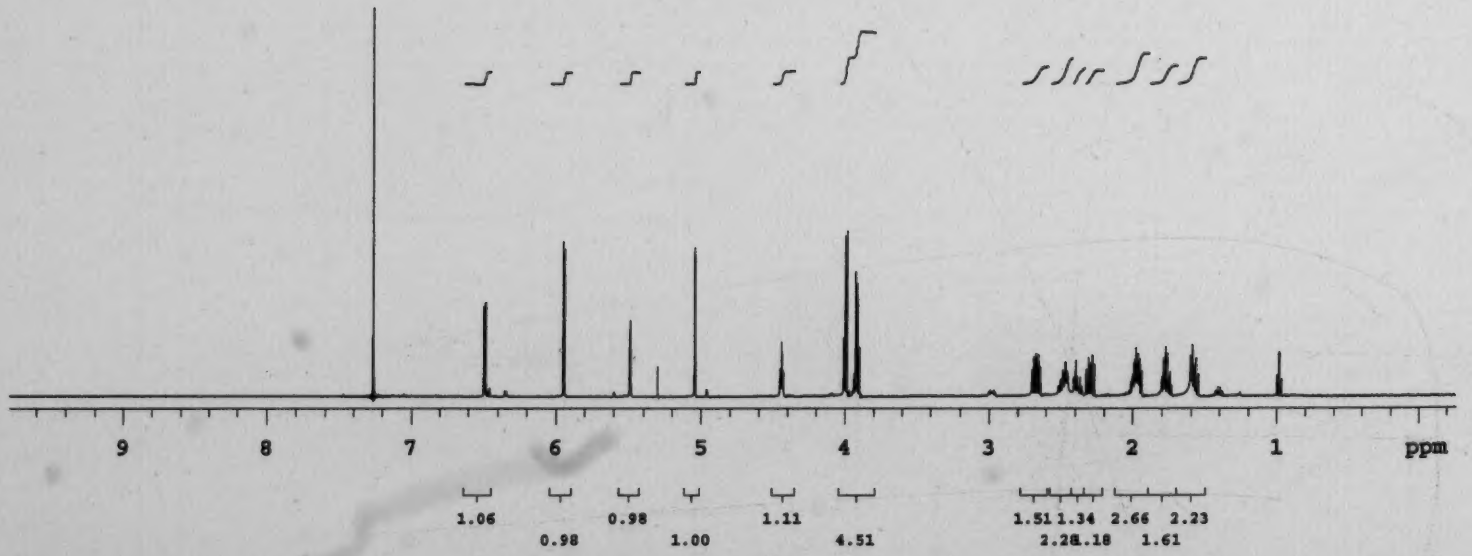
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2
1
ppm
1.06
0.98
0.98
1.00
1.11
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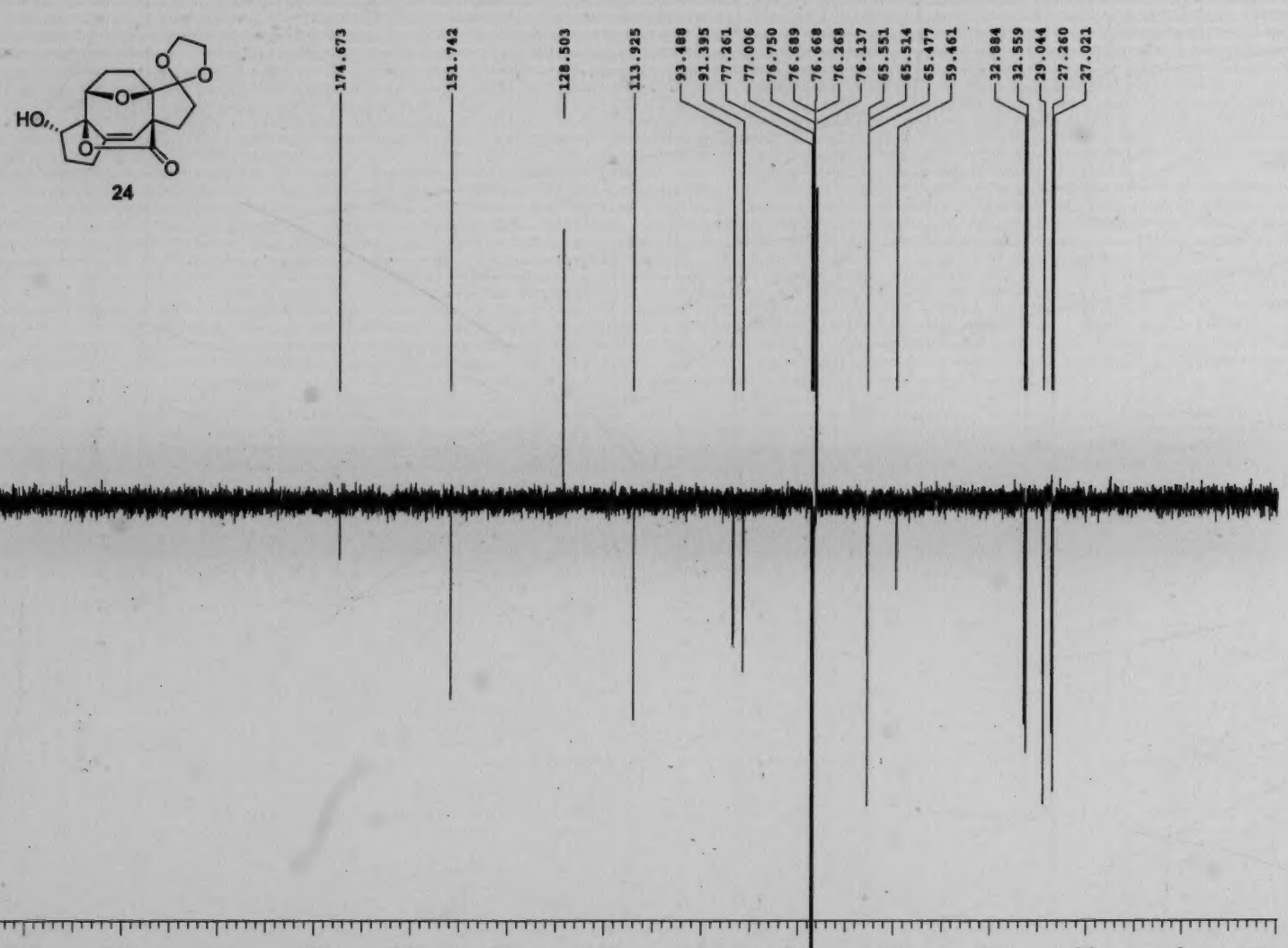
1.51
1.34
2.66
2.23
2.28
1.18
1.61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O
O
O
O
O
O
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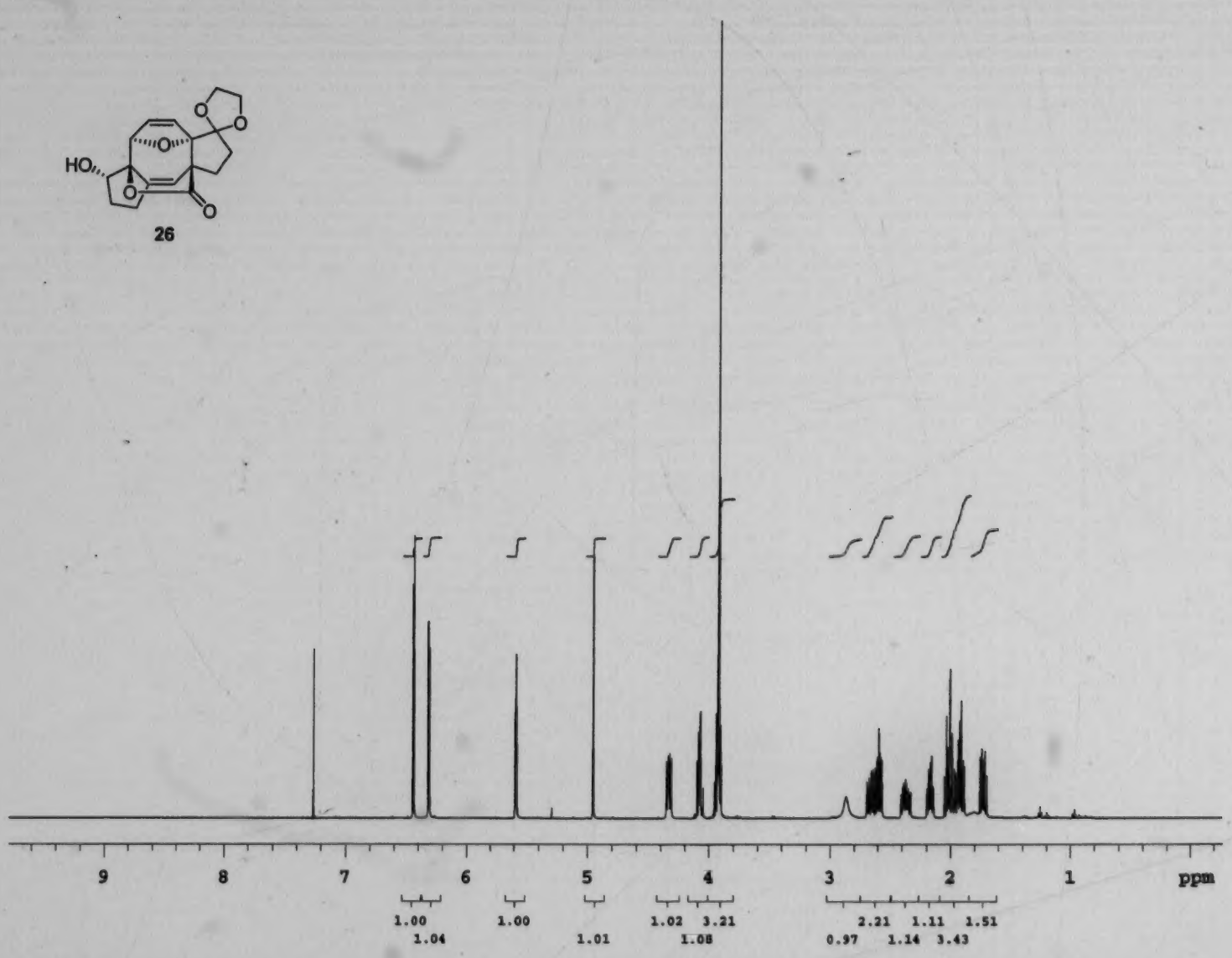
128.503
113.925
93.488
91.395
77.261
77.006
76.750
76.689
76.668
76.268
76.137
65.551
65.514
65.477
59.461
32.884
32.559
29.044
27.260
27.021
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HO
O
O
O
O
O

26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8
7
6
5
4
3
2
1
ppm
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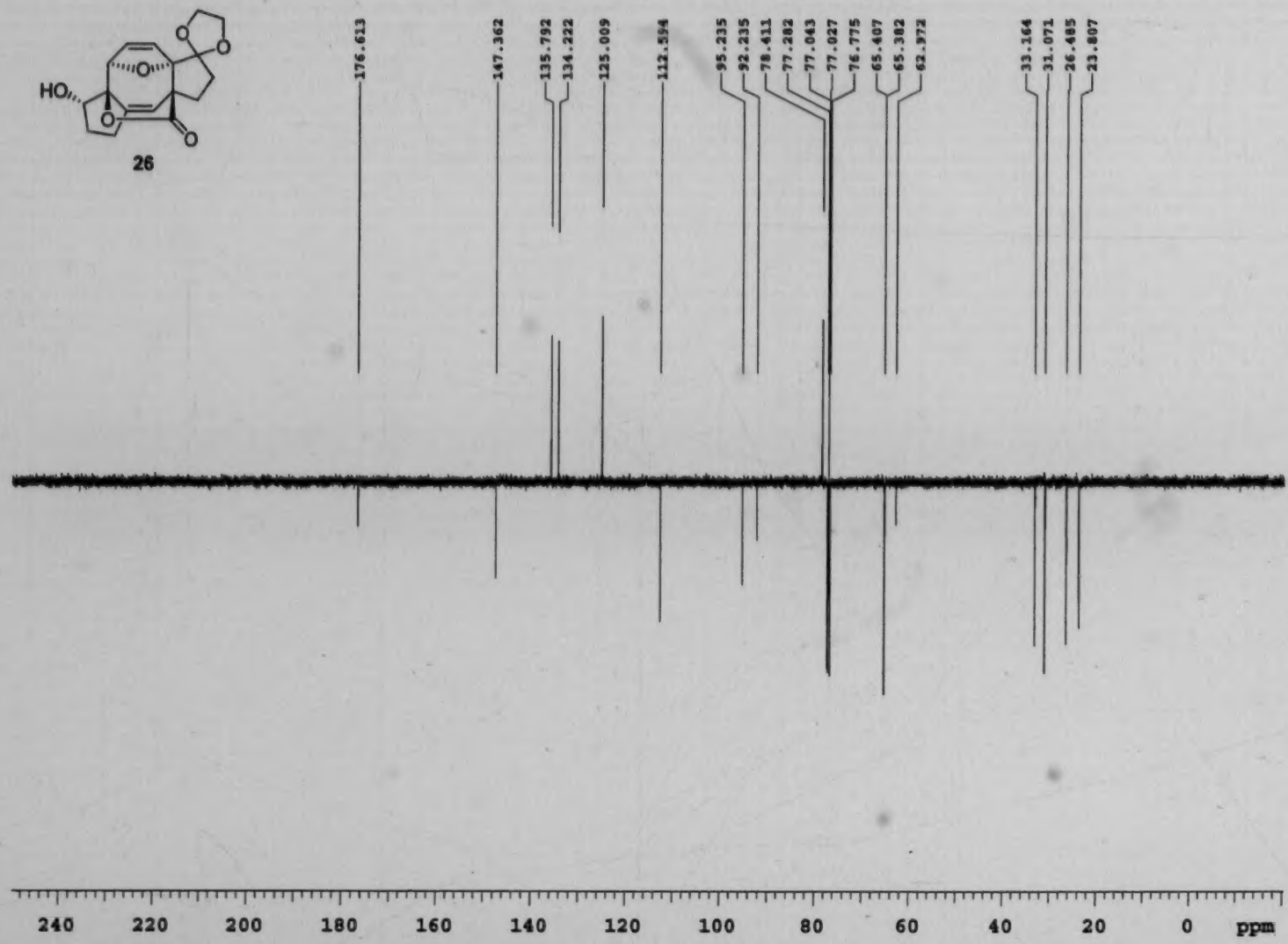
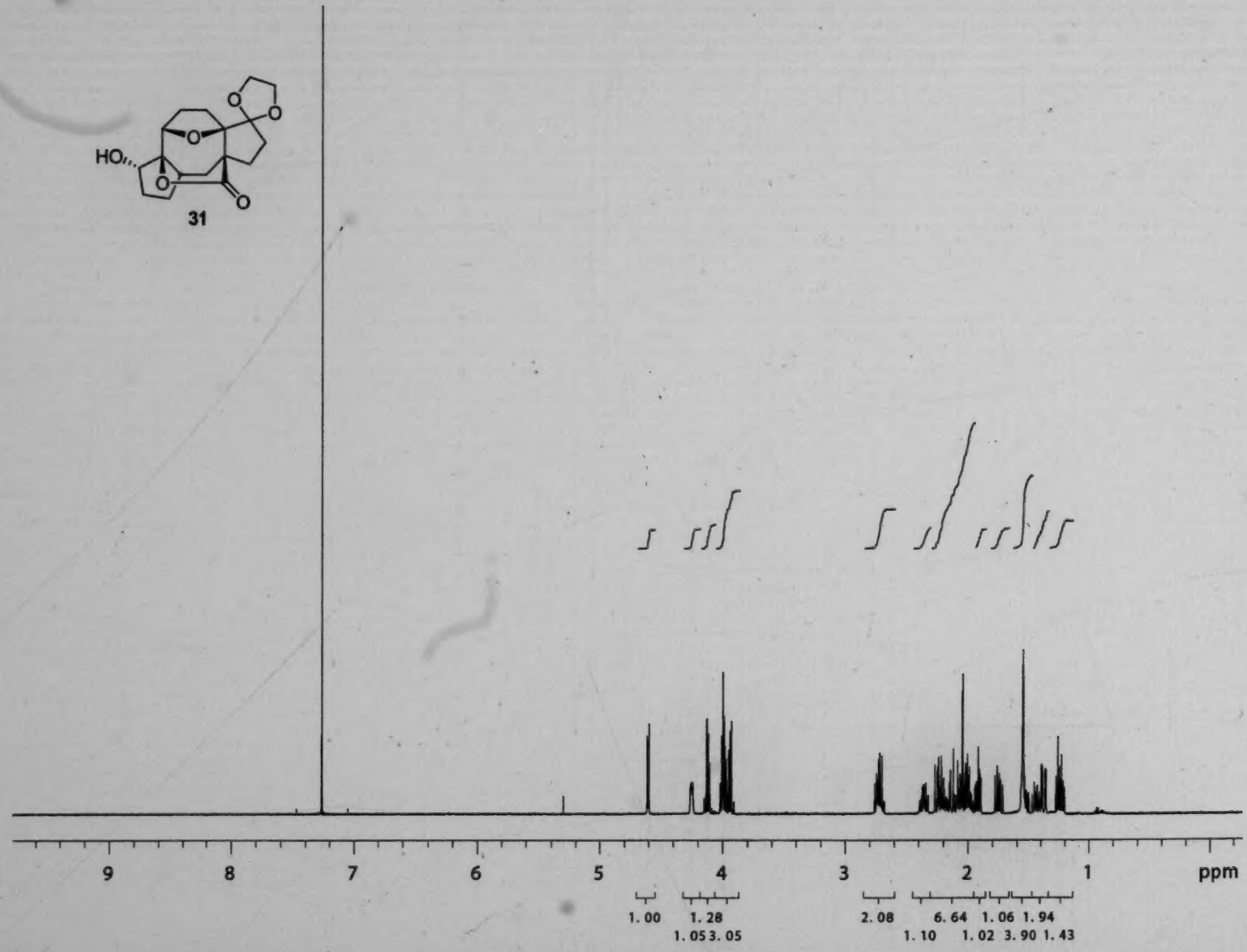
1.00
1.01
1.02
3.21
1.08
0.97
2.21
1.14
1.11
3.43
1.51


HO
O
O
O
O
O
26
176.613
147.362
135.792
134.222
125.009
112.584
95.235
92.235
78.411
77.282
77.043
77.027
76.775
65.407
65.382
62.972
33.164
31.071
26.485
23.807
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HO
O
O
O
O
O

31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8
7
6
5
4
3
2
1
ppm
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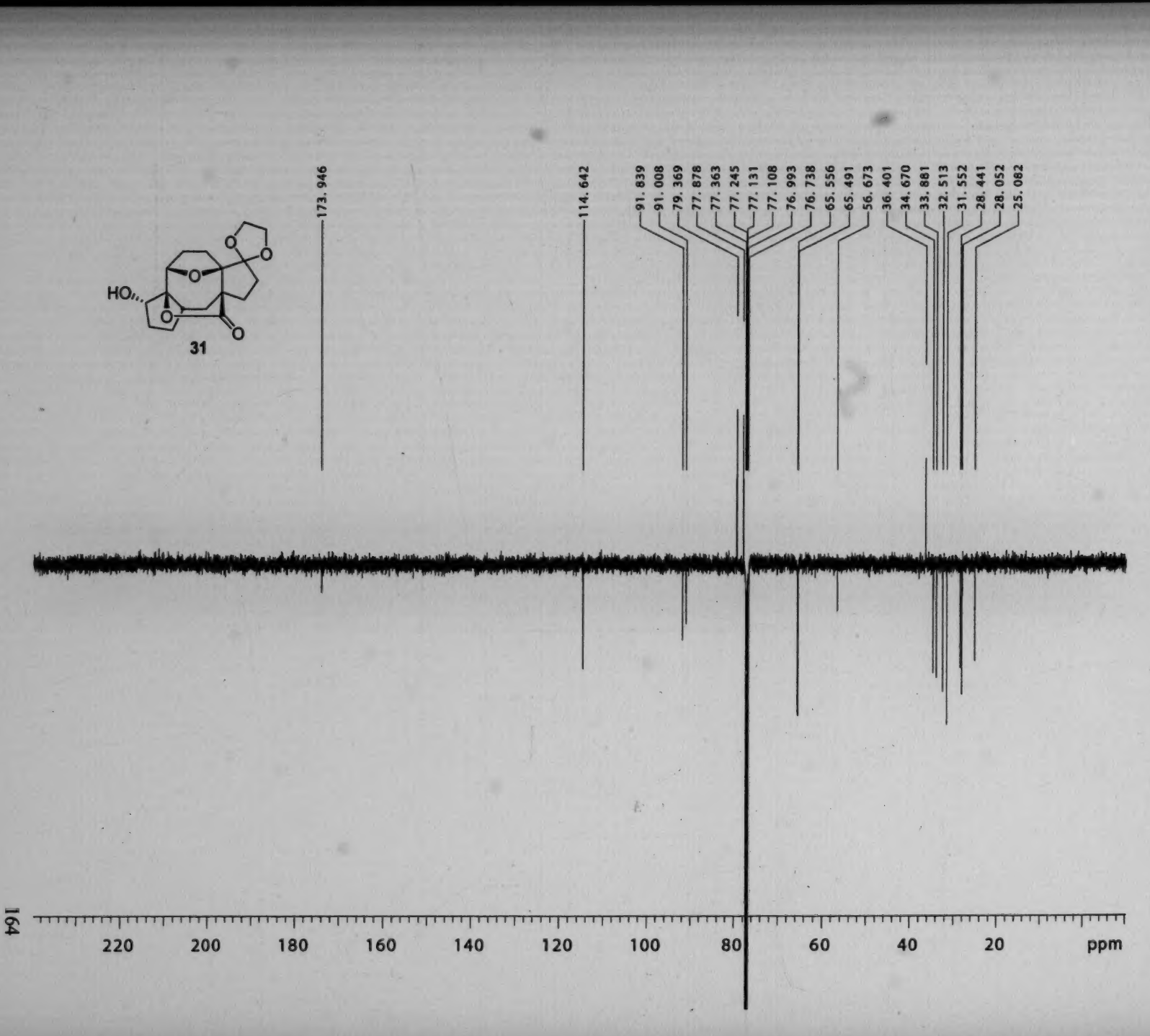
1.28
1.05 3.05
2.08
6.64
1.06
1.94
1.10
1.02
3.90
1.43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O
O
O
O
O
O
31
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91.008
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77.878
77.363
77.245
77.131
77.108
76.993
76.738
65.556
65.491
56.673
36.401
34.670
33.881
32.513
31.552
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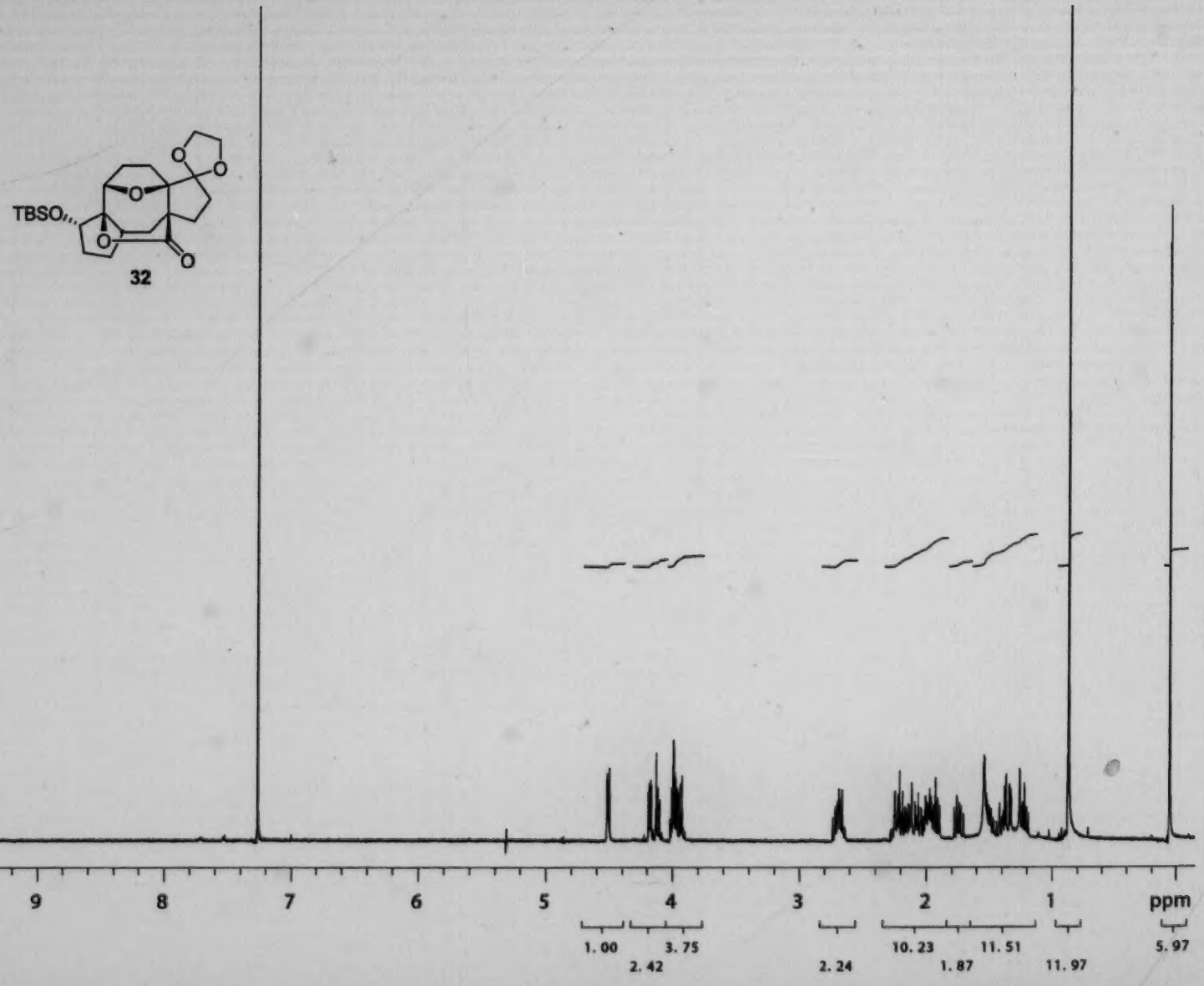
28.052
25.082
220
200
180
160
140
120
100
80
60
40
20
ppm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O
O
O
O
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8
7
6
5
4
3
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ppm
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10.23
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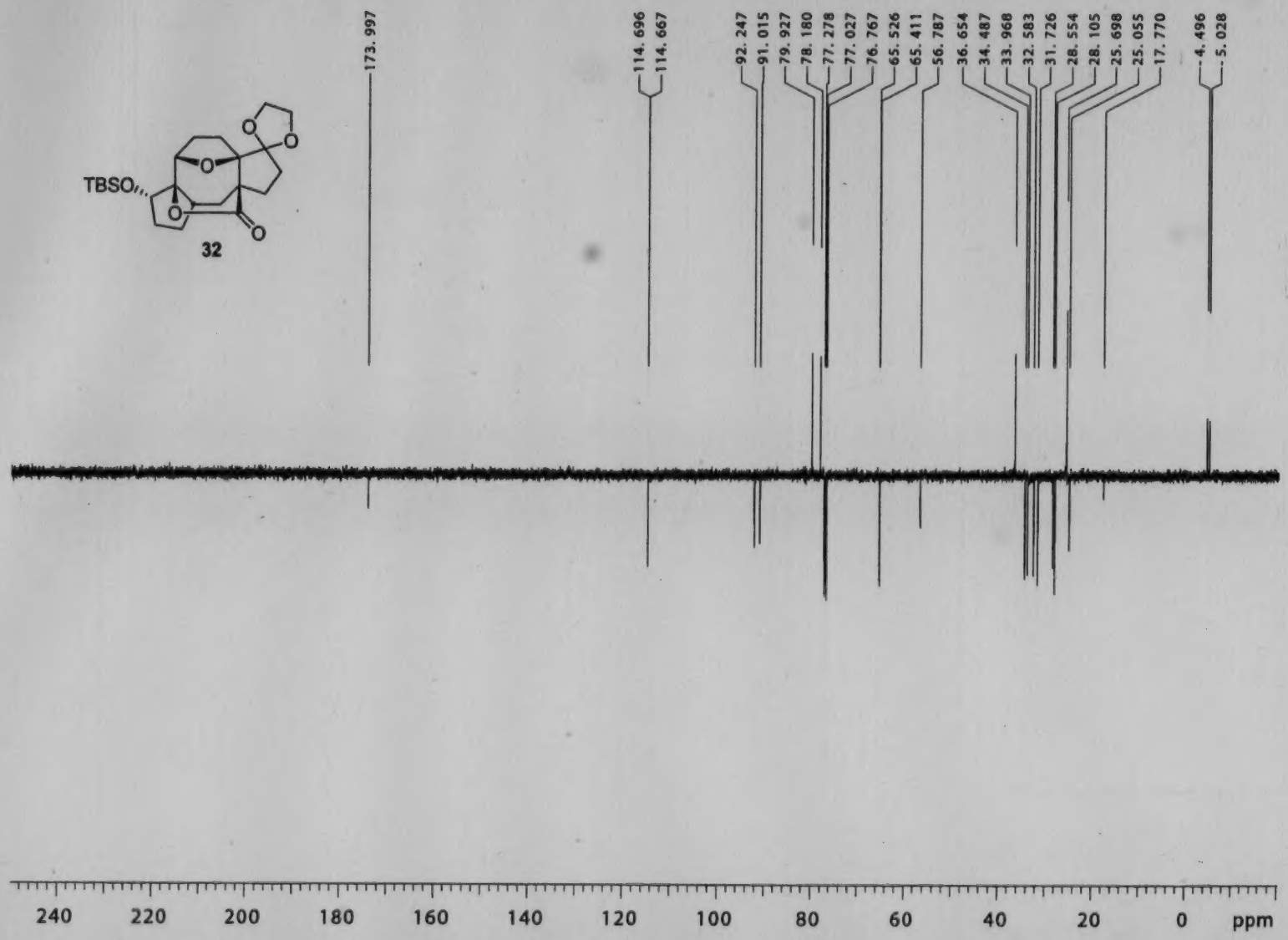
11.97
5.97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O
O
O
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O
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114.667
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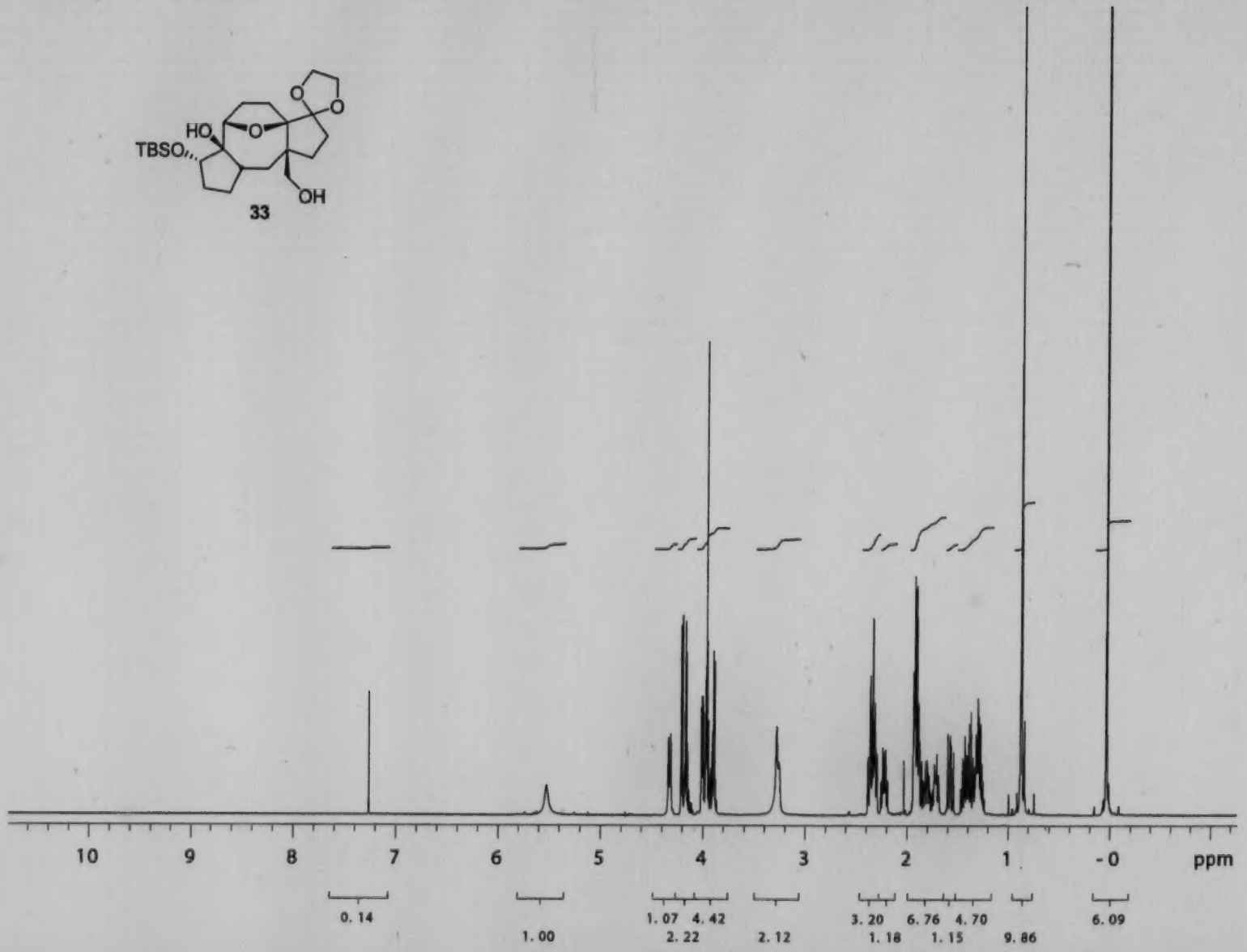
91.015
79.927
78.180
77.278
77.027
76.767
65.526
65.411
56.787
36.654
34.487
33.968
32.583
31.726
28.554
28.105
25.698
25.055
17.770
4.496
5.028
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HO
TBSO
O
O
O
OH

33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8
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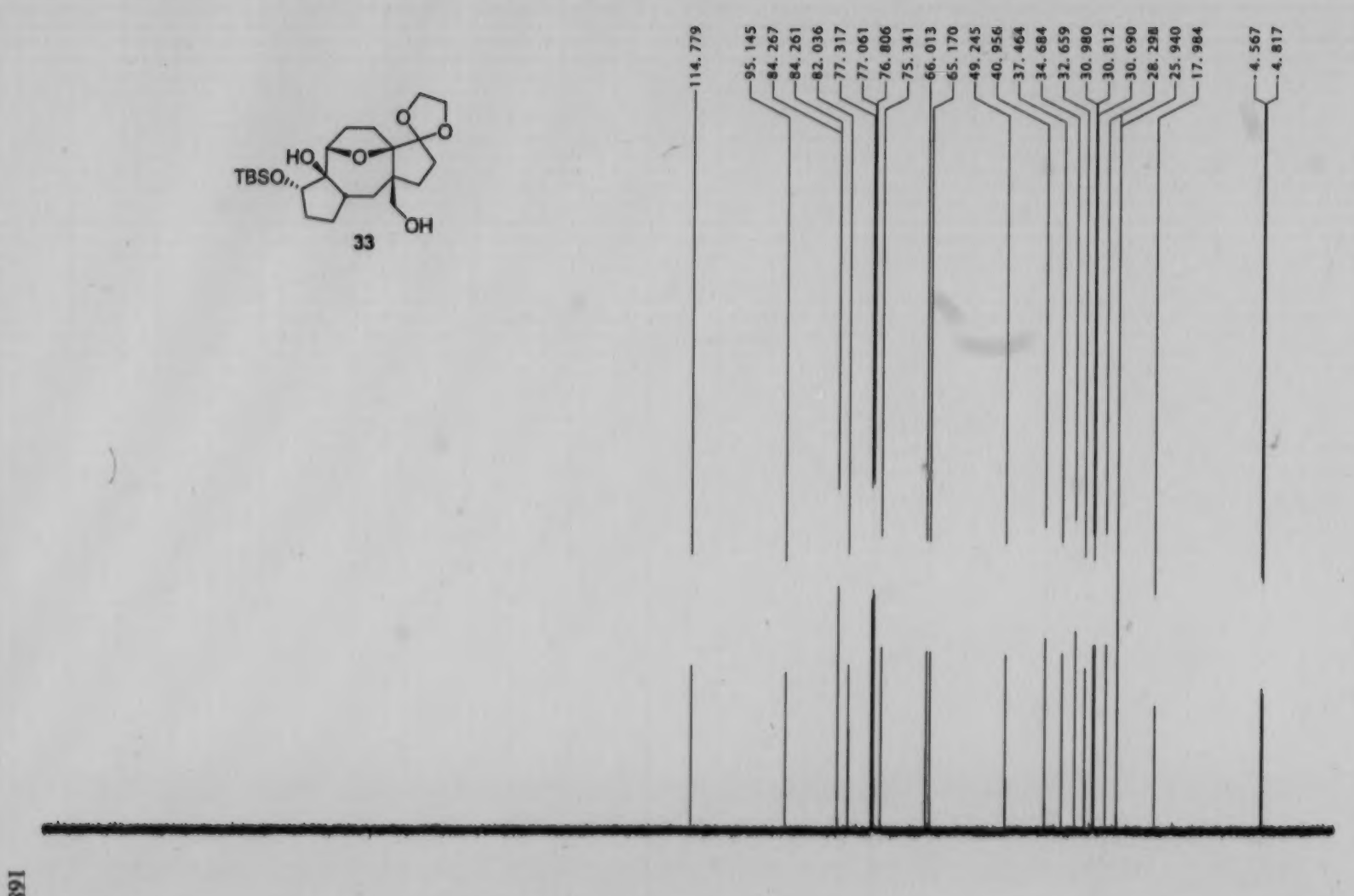
6
5
4
3
2
1
-0
ppm
0. 14
1. 00
1. 07
4. 42
2. 22
2. 12
3. 20
6. 76
4. 70
1. 18
1. 15
9. 86
6. 09

HO
TBSO
O
O
O
OH

33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82.036
77.317
77.061
76.806
75.341
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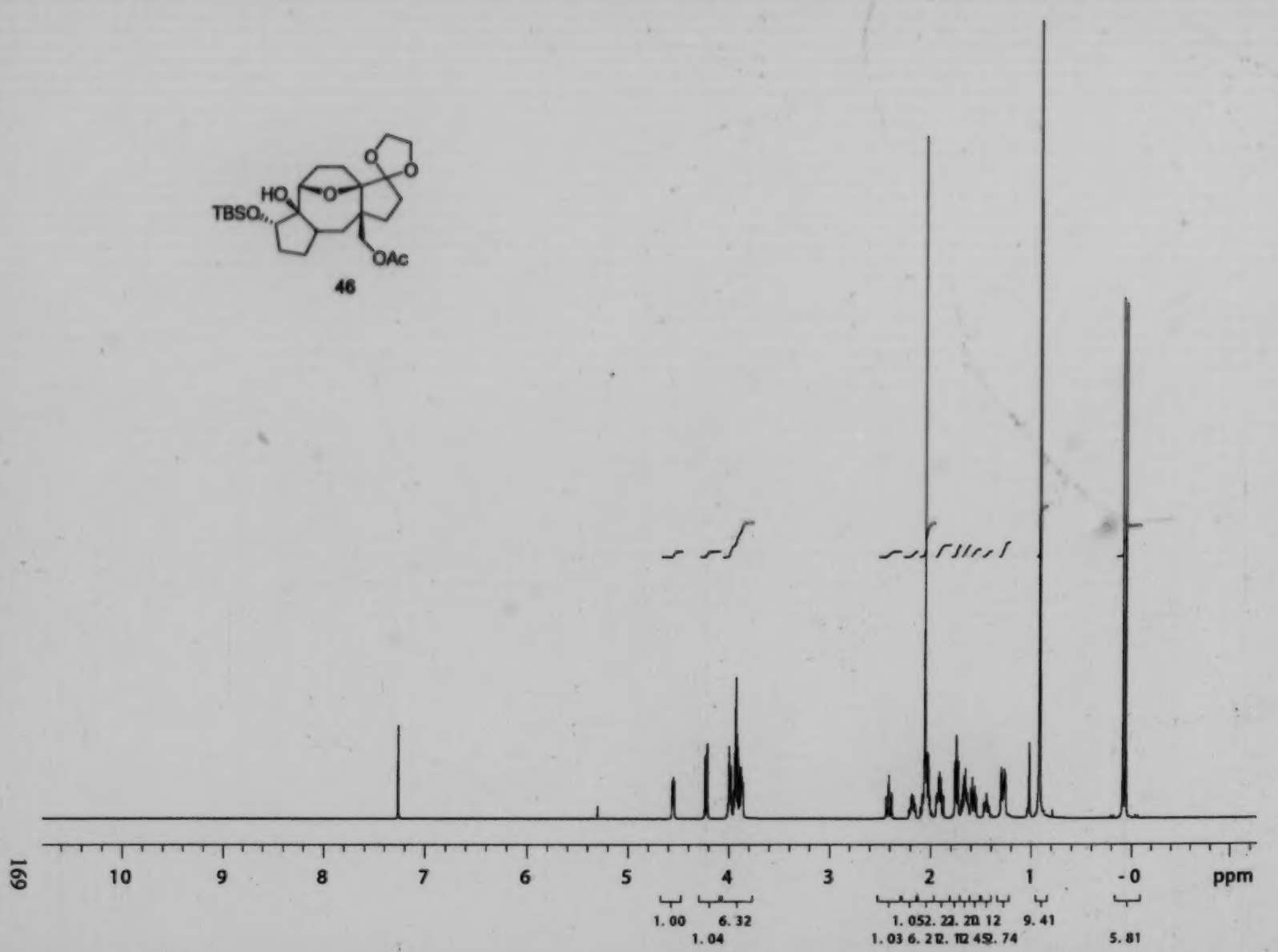
65.170
49.245
40.958
37.464
34.684
32.659
30.980
30.812
30.690
28.298
25.940
17.984
4.567
4.817
891
168
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HO
TBSO
O
O
O
OAc

46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7
6
5
4
3
2
1
-0
ppm
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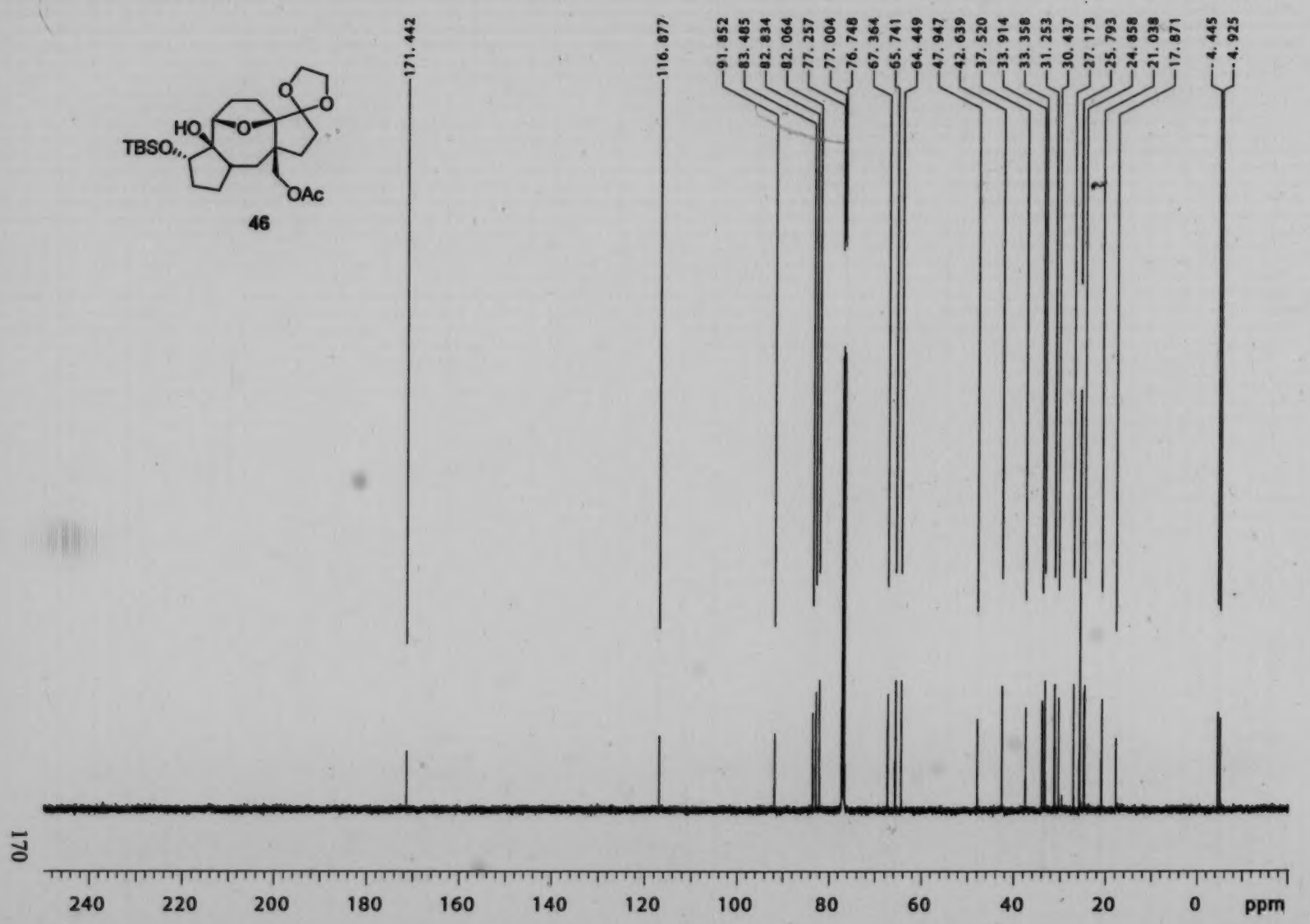
6.32
1.04
1.05
2.23
2.21
2.12
9.41
1.03
6.21
2.10
2.12
4.52
2.74
5.81

HO
TBSO
O
O
O
OAc

46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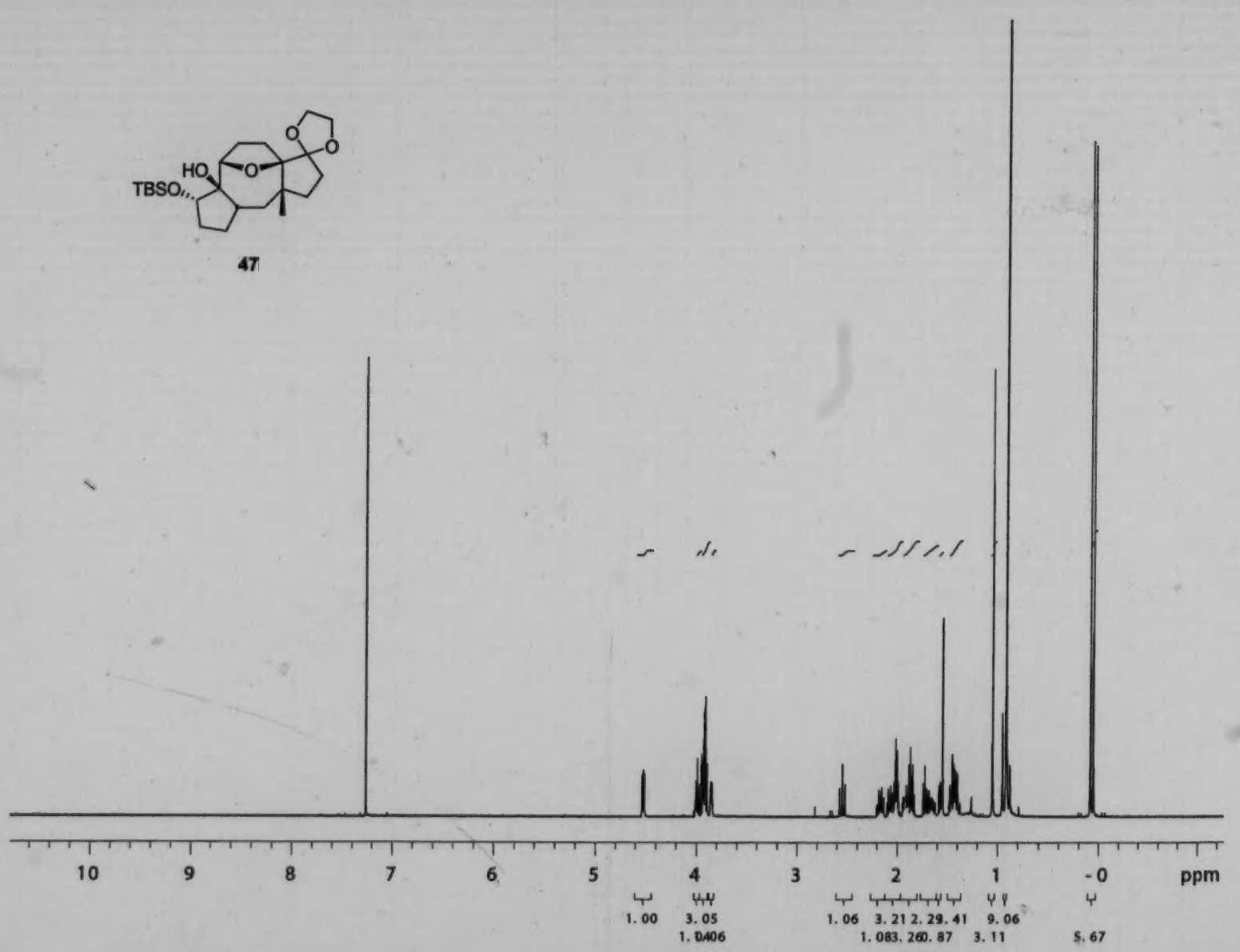
82.064
77.257
77.004
76.748
67.364
65.741
64.449
47.947
42.639
37.520
33.914
33.358
31.253
30.437
27.173
25.793
24.858
21.038
17.871
4.445
4.925
170
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HO
TBSO
O
O
O

47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7
6
5
4
3
2
1
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1.0406
1.06
3.21
2.29
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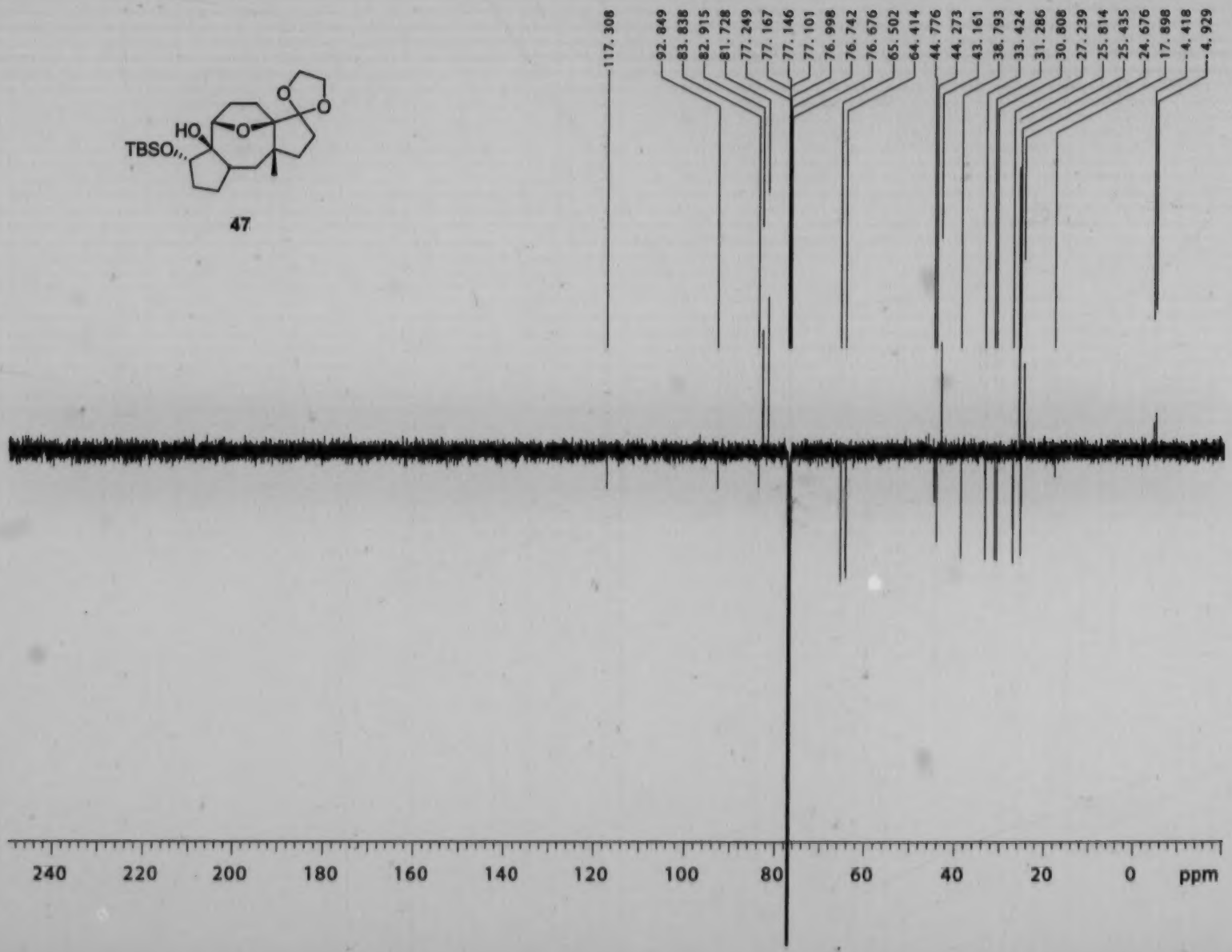
1.083.26
0.87
3.11
5.67

HO
TBSO
O
O
O

47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82.915
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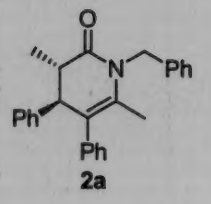
77.249
77.167
77.146
77.101
76.998
76.742
76.676
65.502
64.414
44.776
44.273
43.161
38.793
33.424
31.286
30.808
27.239
25.814
25.435
24.676
17.898
-4.418
-4.929
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

APPENDIX B

CHAPTER 3 NMR SPECTRA



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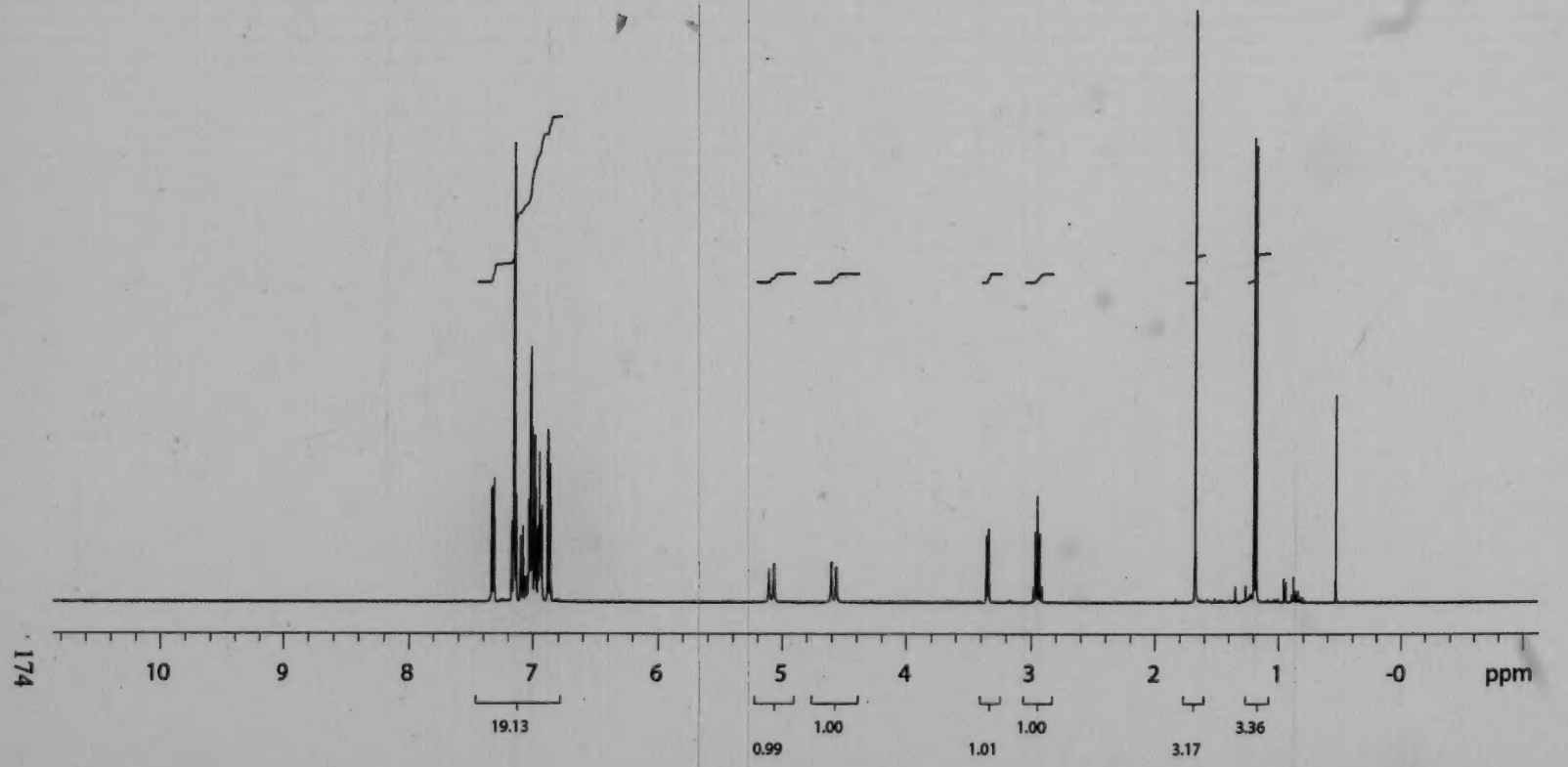

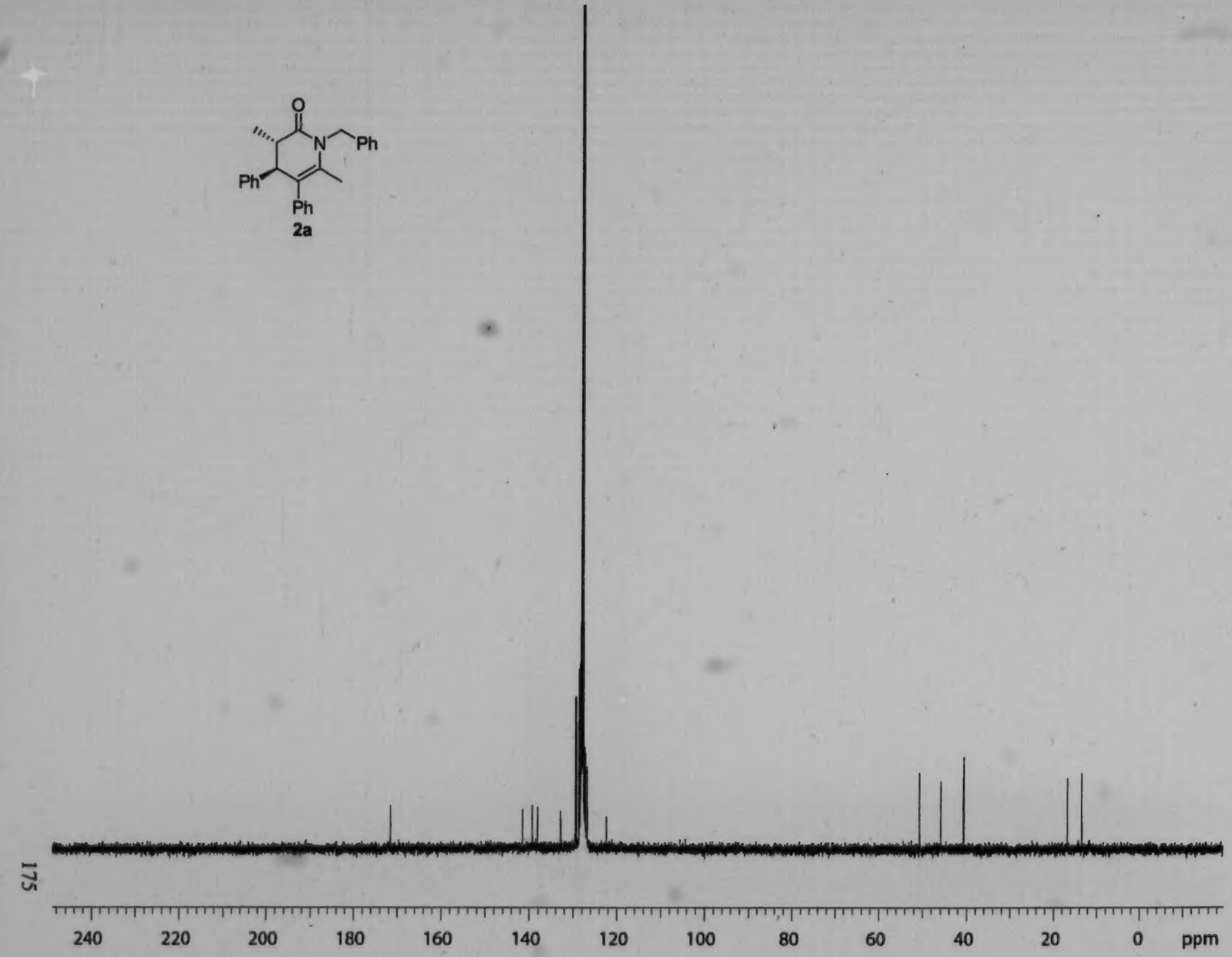
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N
Ph
Ph
Ph
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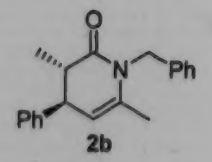
200
180
160
140
120
100
80
60
40
20
0
ppm



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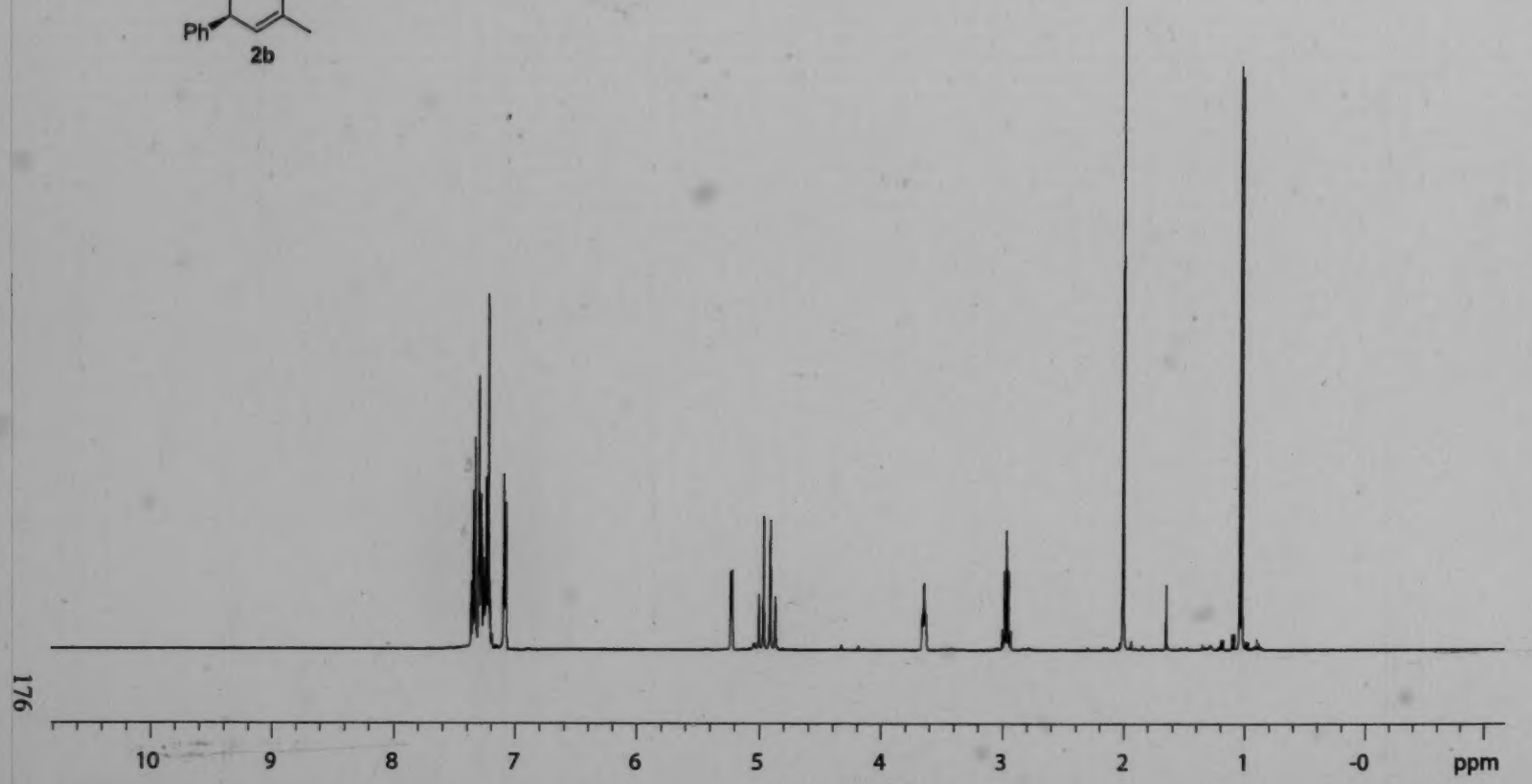

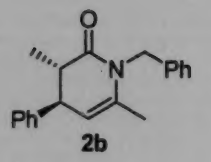

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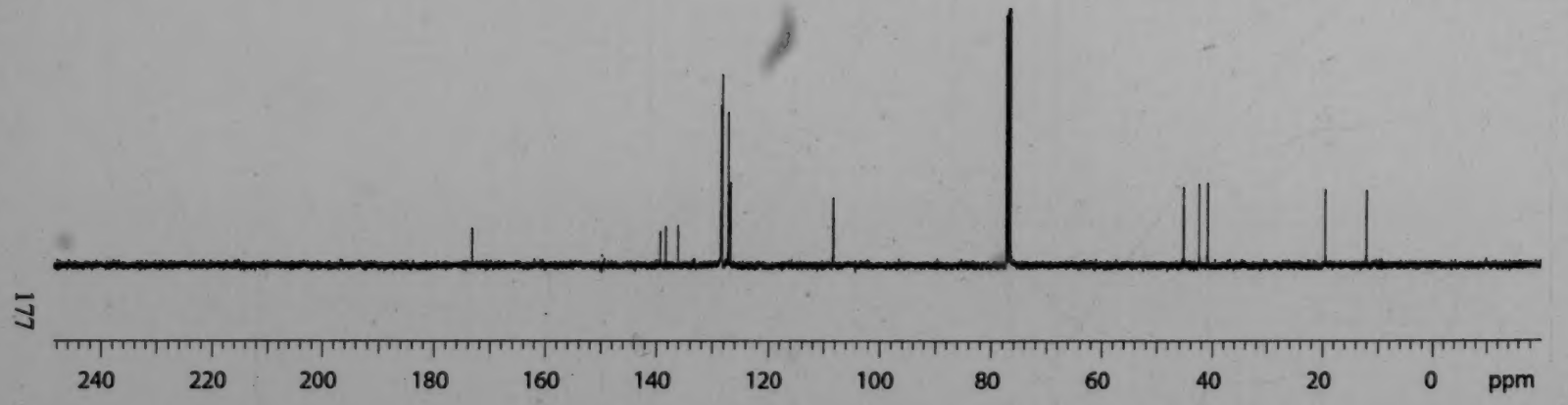

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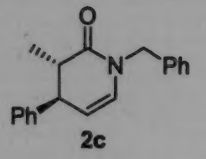

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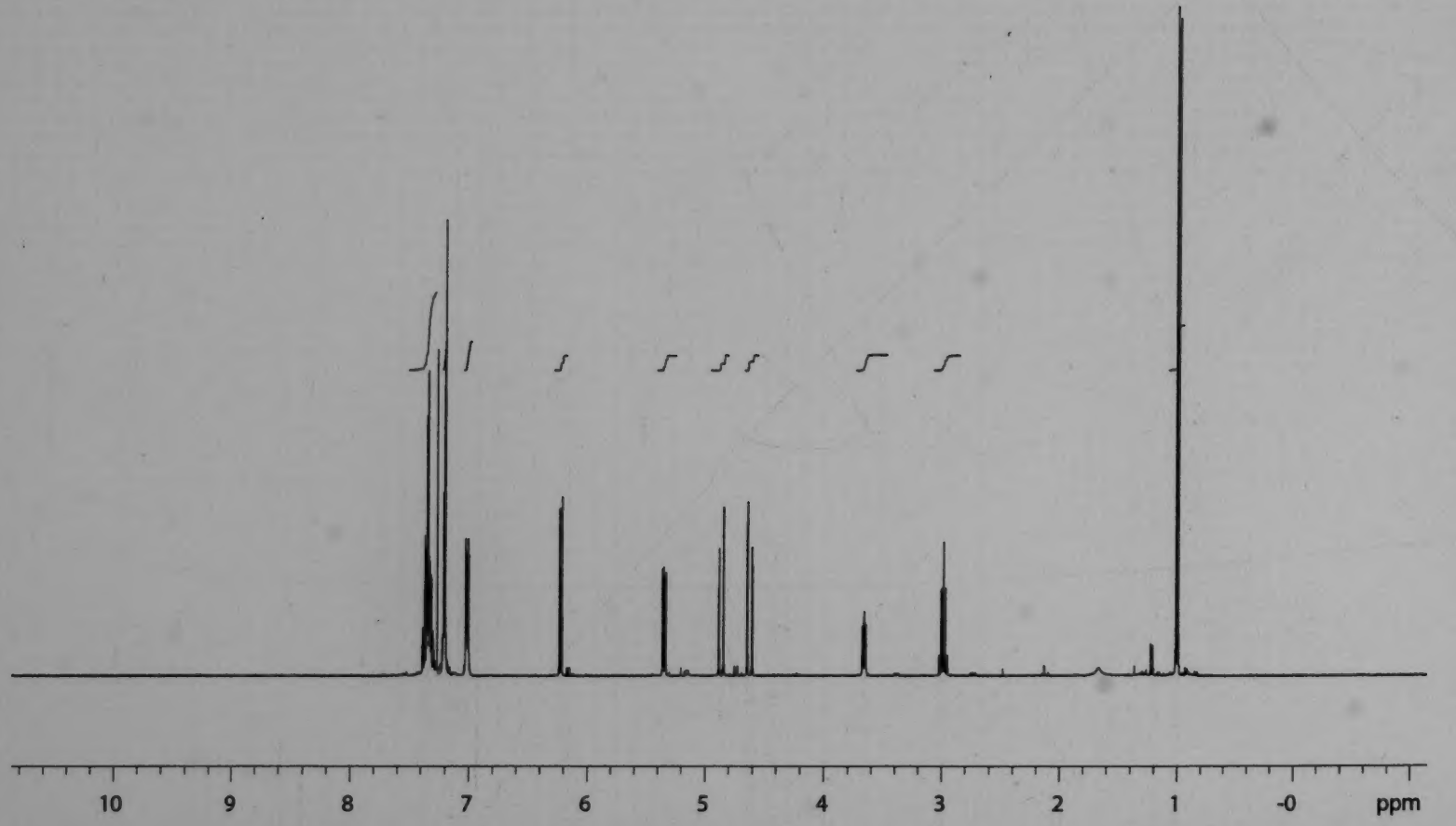

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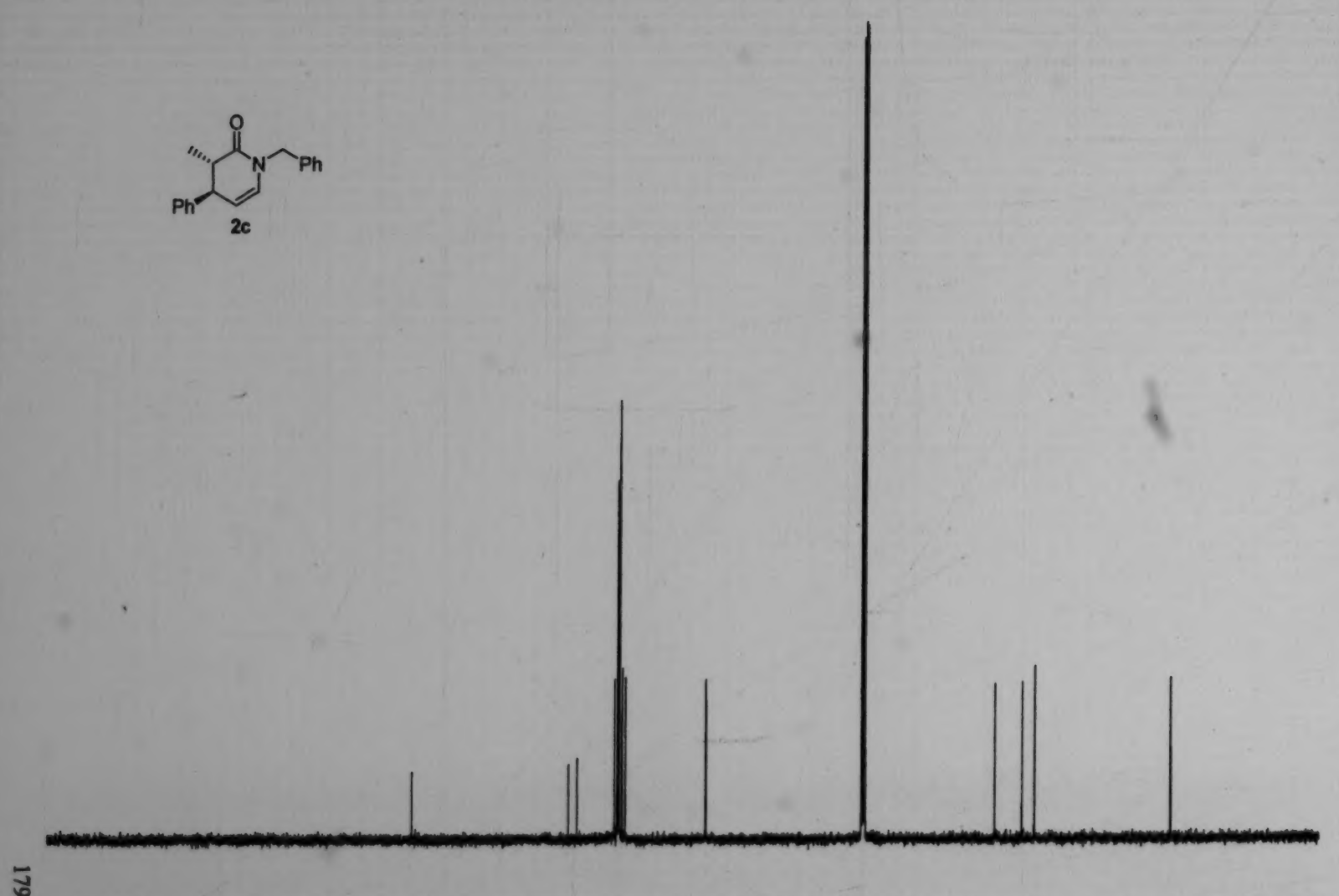

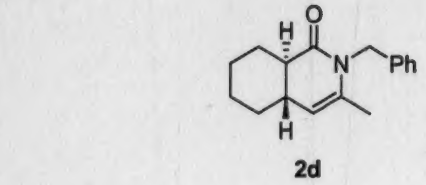

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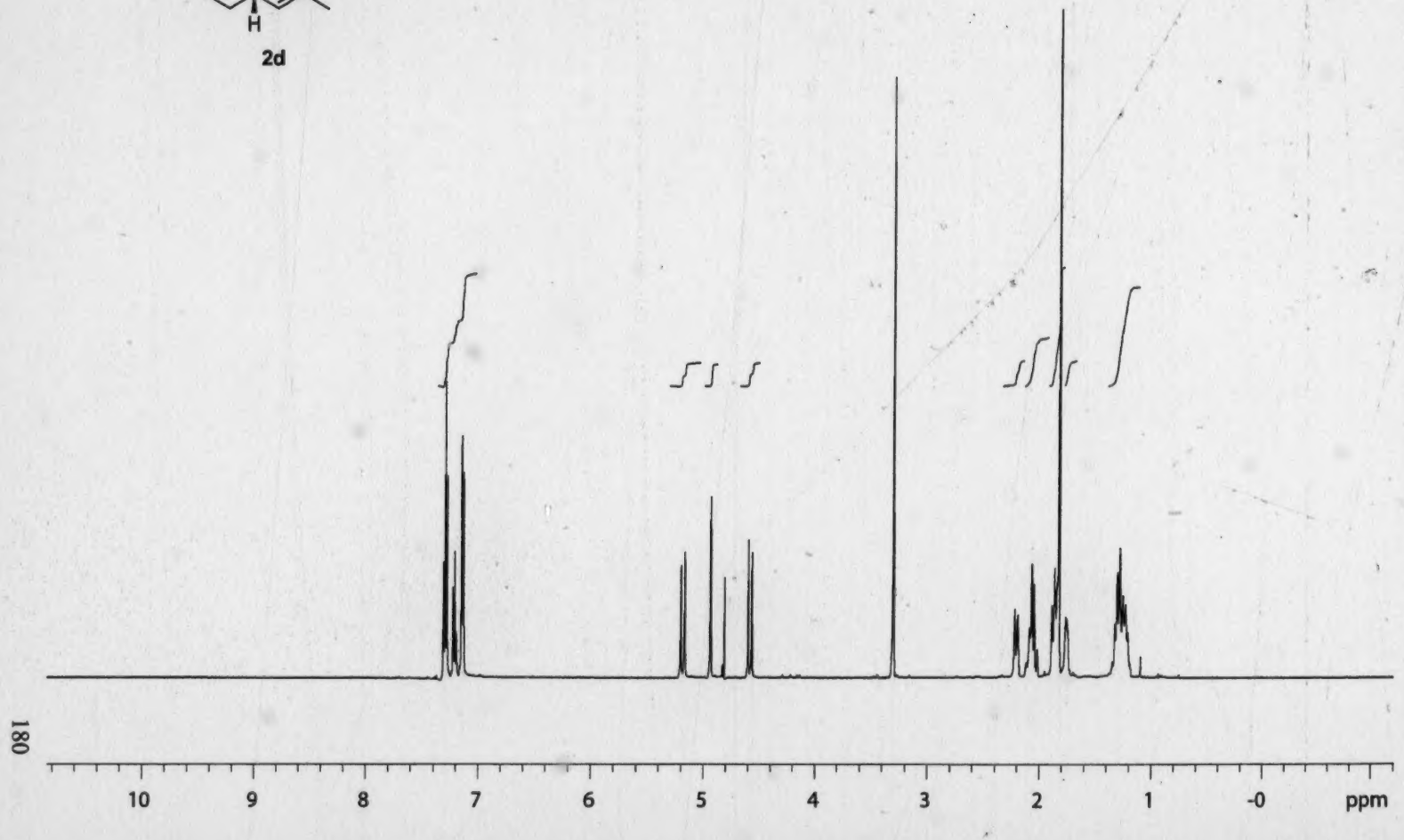

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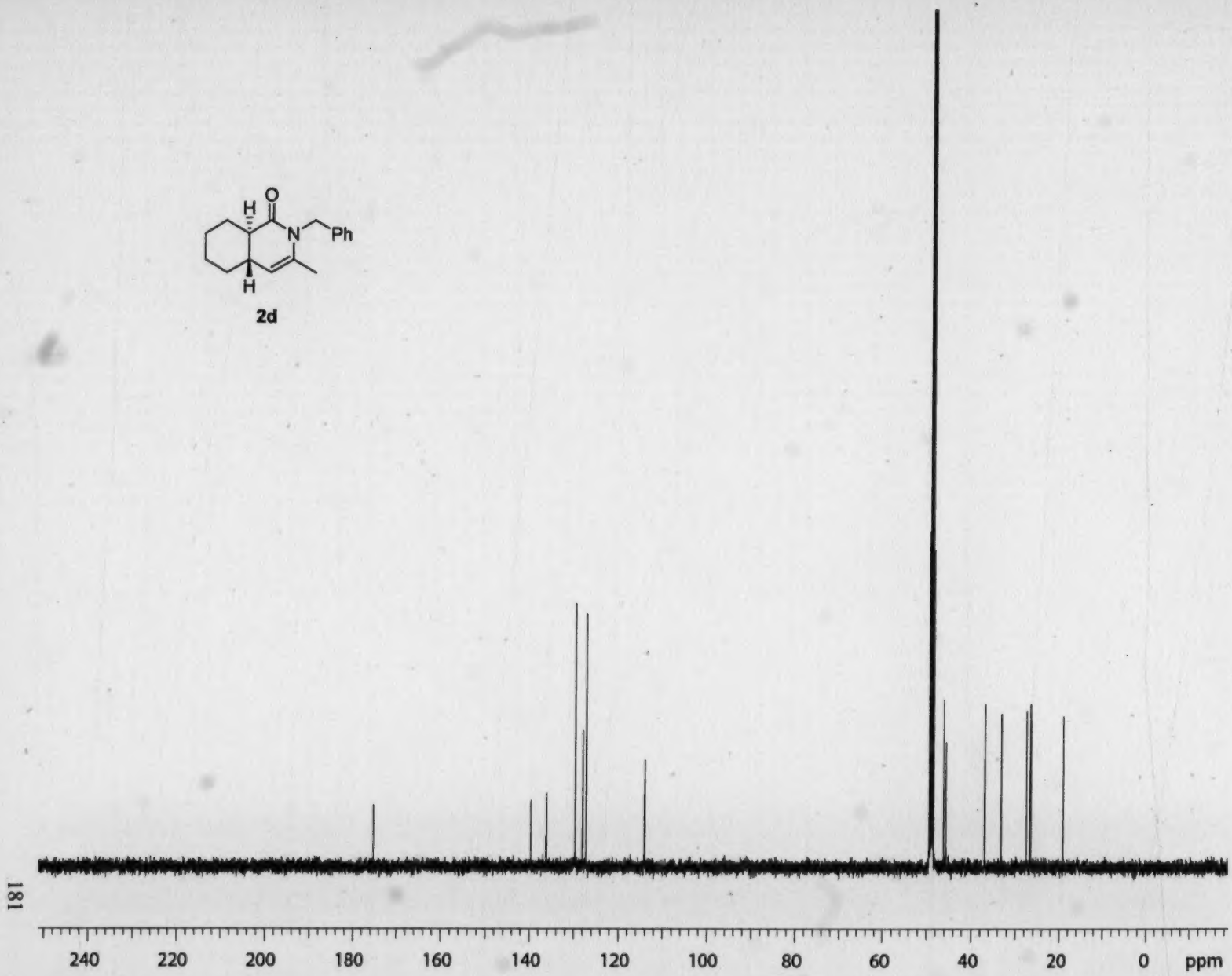

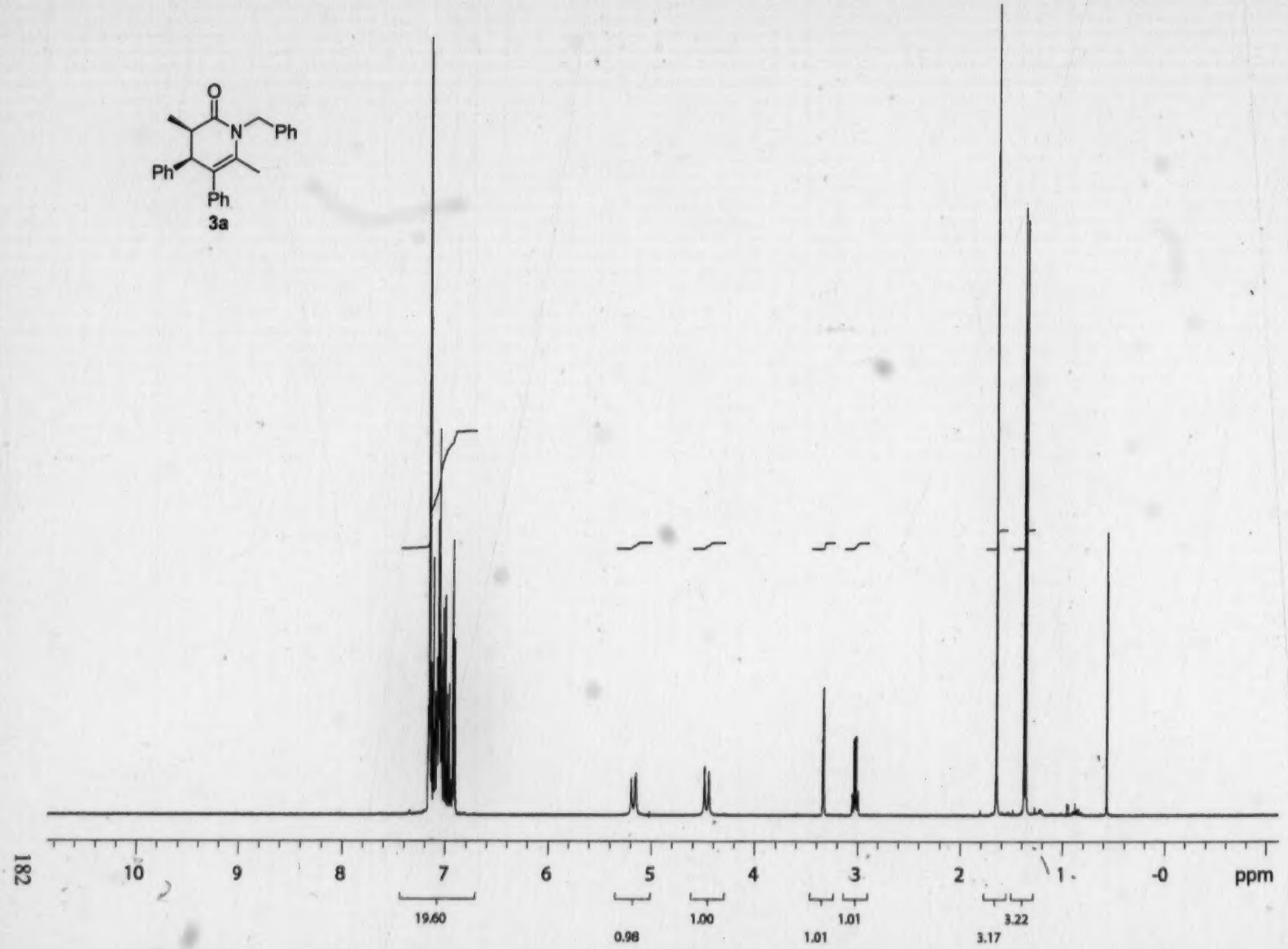
O
N
Ph
Ph
Ph
3a
182
10
9
8
7
6
5
4
3
2
1
-0
ppm
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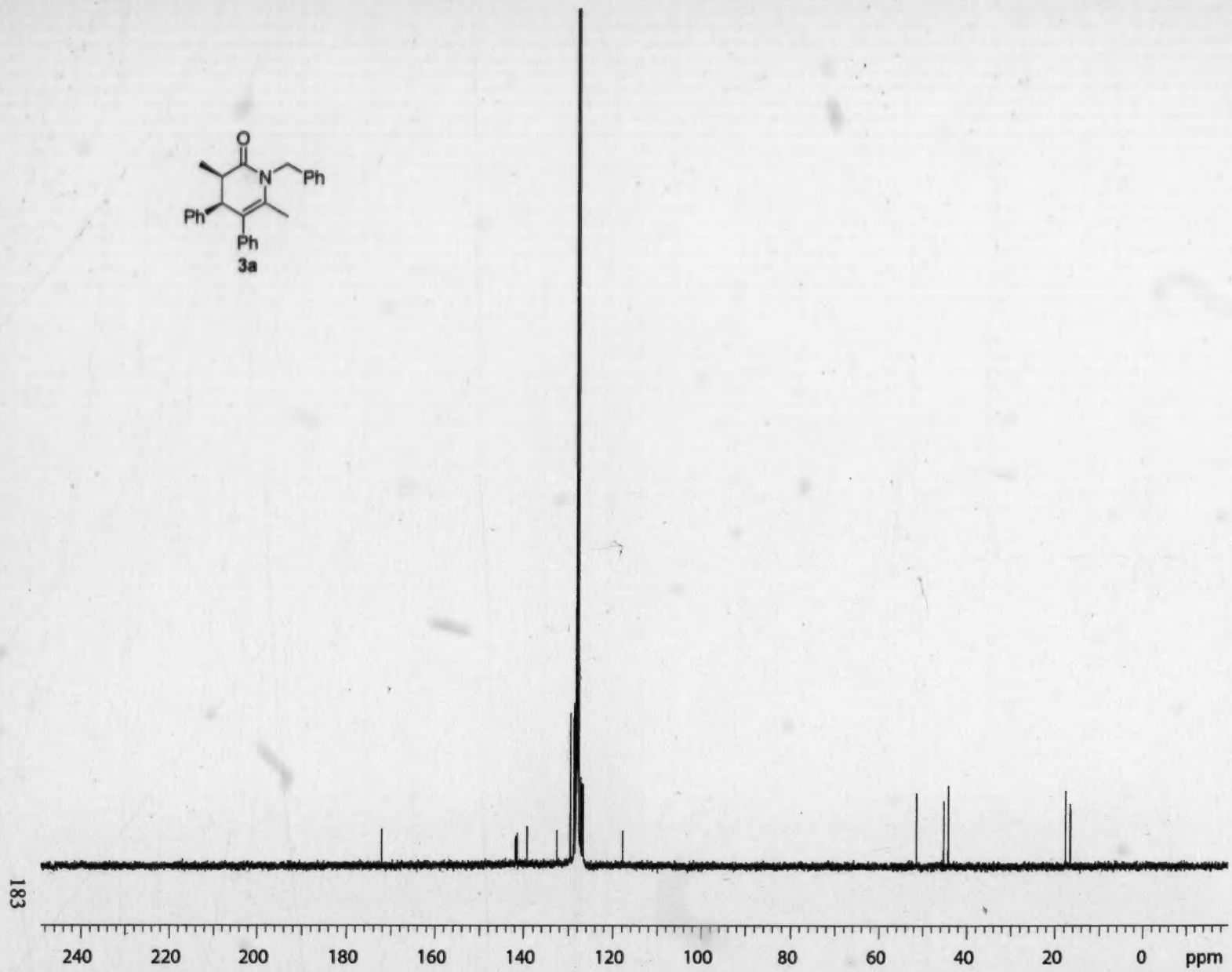
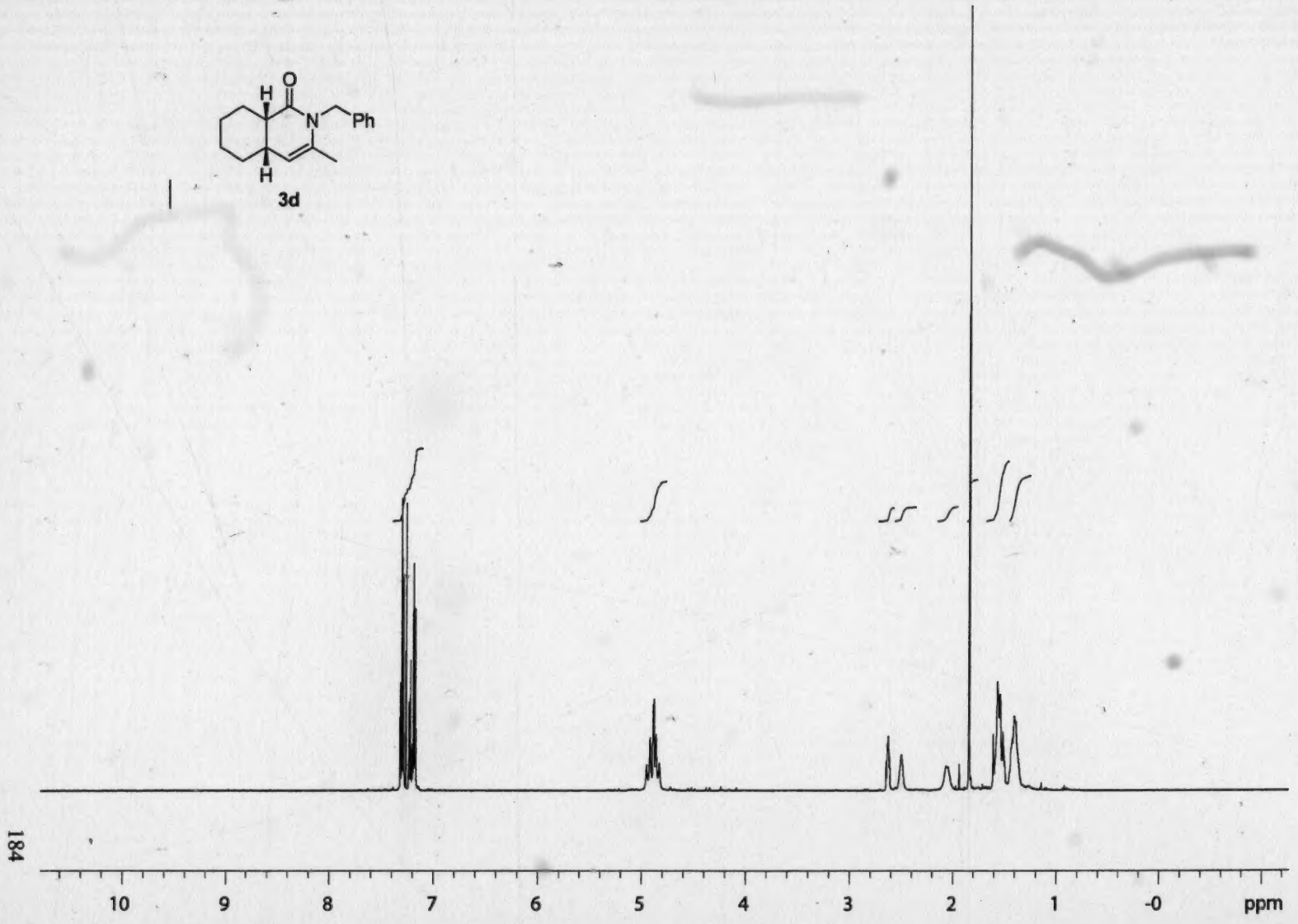
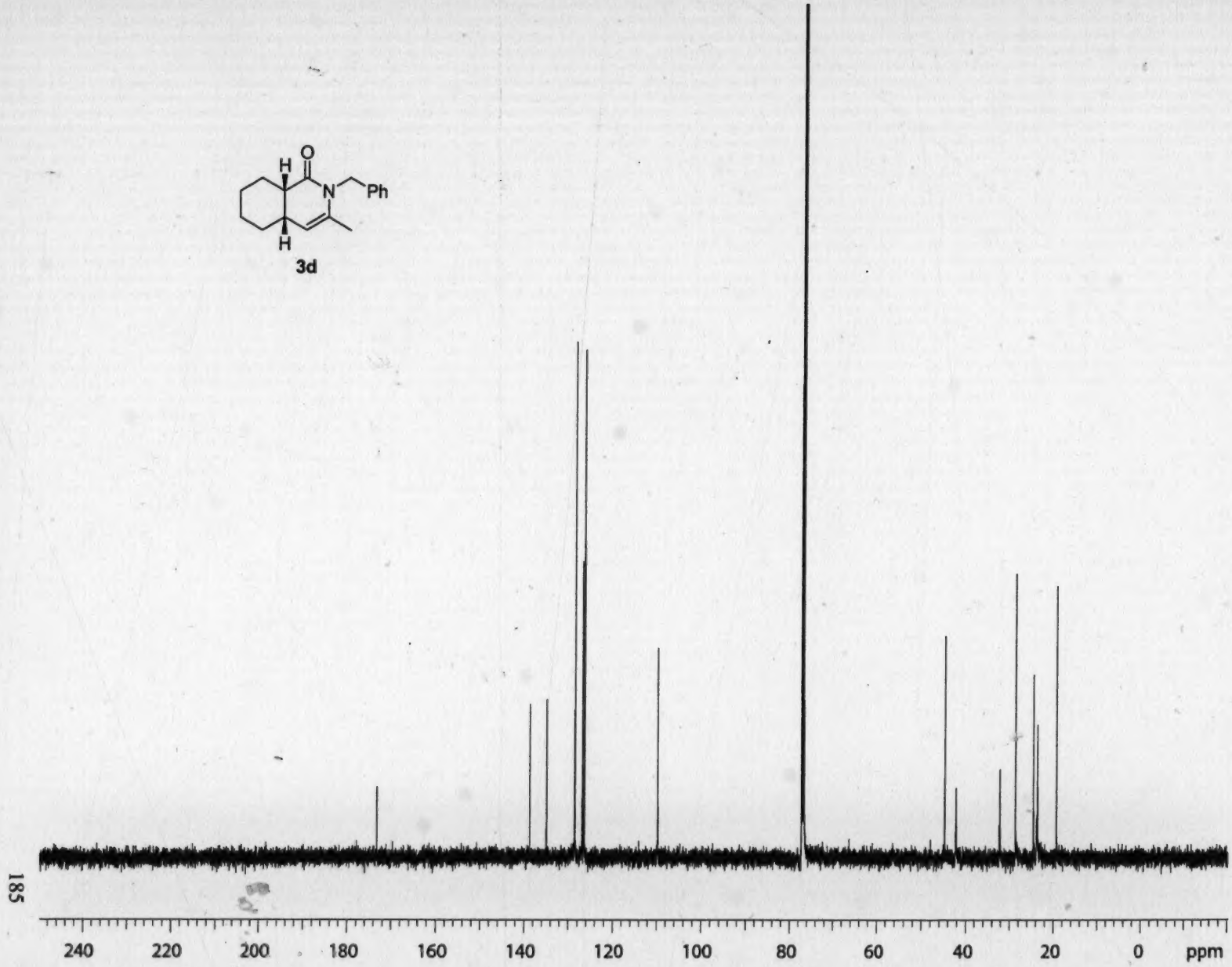
0.98
1.00
1.01
1.01
3.17
3.22


O
N
Ph
Ph
Ph
3a
183
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
H
N
Ph
H
3d
184
10
9
8
7
6
5
4
3
2
1
-0
ppm

3d



APPENDIX C

X-RAY CRYSTALLOGRAPHIC DATA TABLES FOR COMPOUND 24 (CHAPTER 2)

UNIVERSITY OF ALBERTA
X-Ray Crystallography Laboratory
Department of Chemistry • University of Alberta
Edmonton, Alberta T6G 2G2 Canada

Phone: +1 780 492 2485
Fax: +1 780 492 8231

Bob.McDonald@ualberta.ca • Michael.Ferguson@ualberta.ca
http://xray.chem.ualberta.ca/

STRUCTURE REPORT

XCL Code: FGW0501 **Date:** 7 April 2005

Compound: 16,17-Dioxa-4,4-ethylenedioxy-10-hydroxypentacyclo[7.5.2.$1^{5,8}$.$0^{1,5}$.$0^{9,13}$]heptadec-13-en-15-one (*relative stereochemistry*)

Formula: $C_{17}H_{20}O_6$

Supervisor: F. G. West

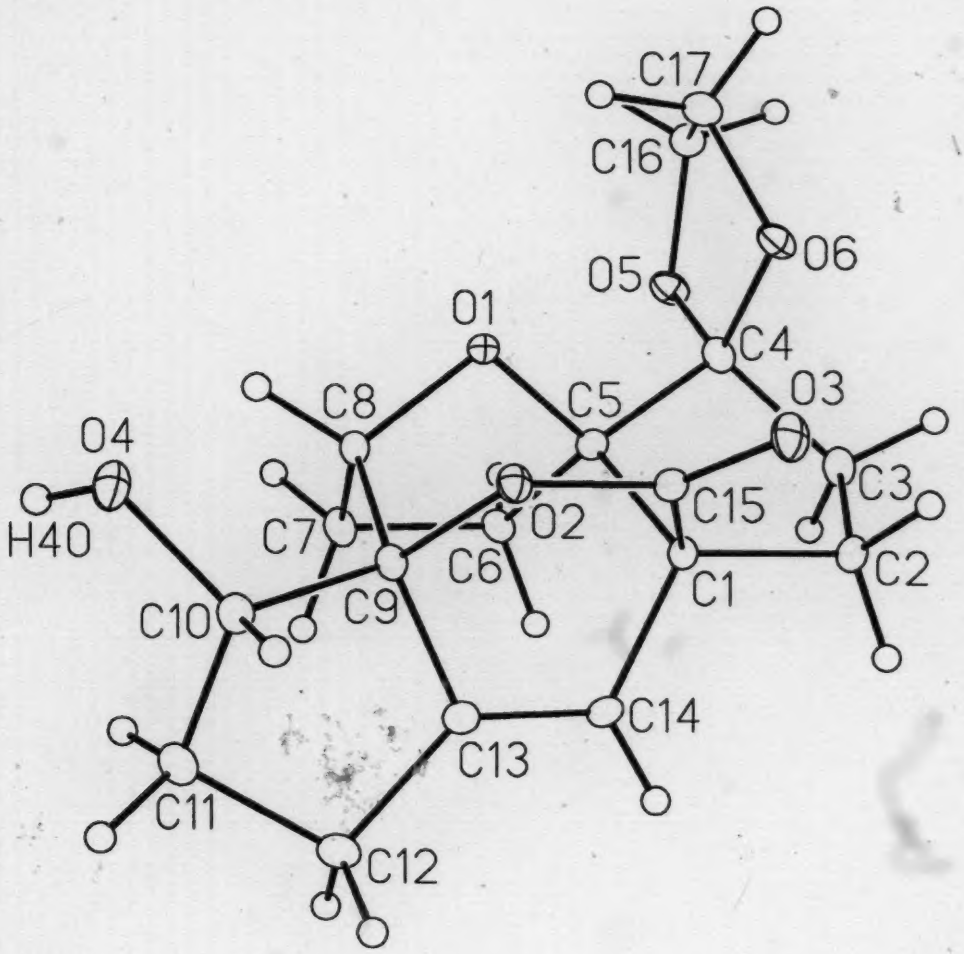
Crystallographer: R. McDonald

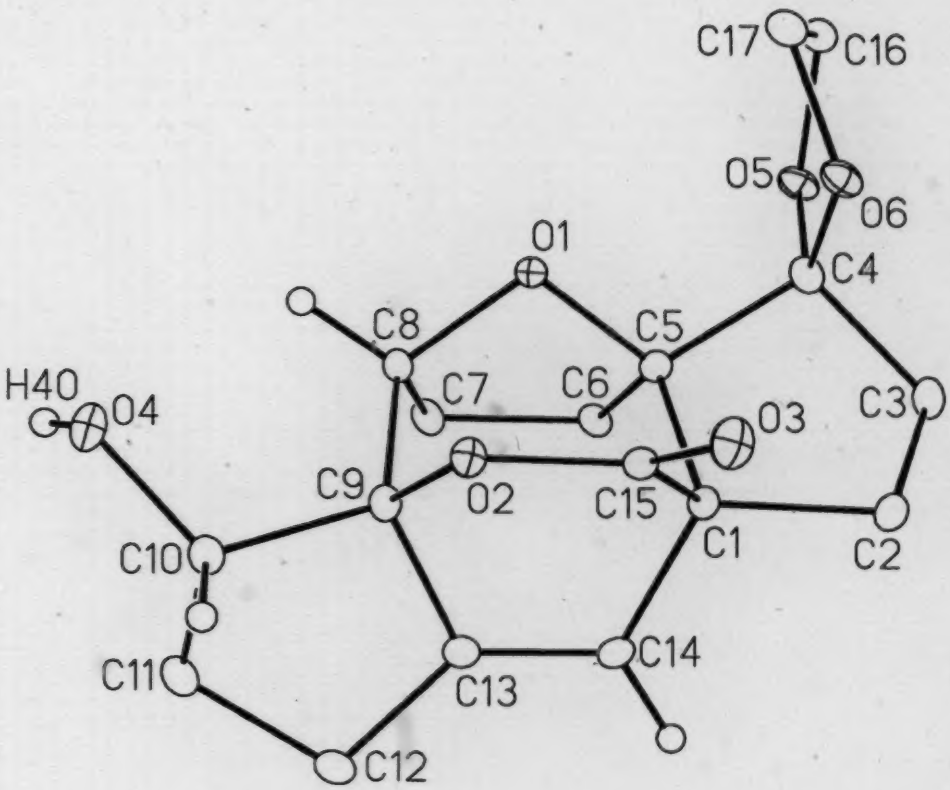
Figure Legends

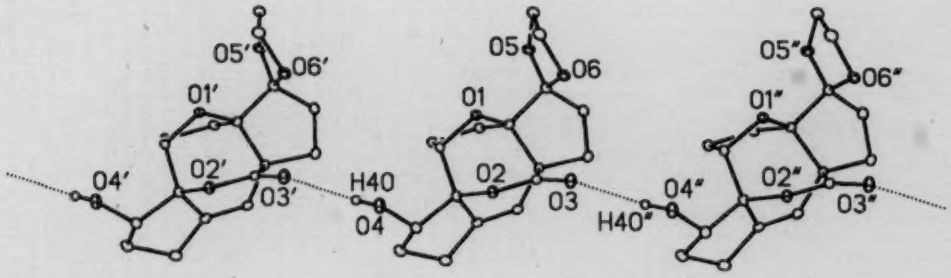
Figure 1. Perspective view of the 16,17-dioxa-4,4-ethylenedioxy-10-hydroxy-pentacyclo[7.5.2.$1^{5,8}$.$0^{1,5}$.$0^{9,13}$]heptadec-13-en-15-one molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Figure 2. Alternate view of the molecule. Hydrogens of methylene groups have been omitted.

Figure 3. Illustration of hydrogen-bonded interactions between adjacent molecules in the unit cell. Molecules are related by translations of one unit-cell-length parallel to the unit cell's *b* axis (*b* = 8.0097 (11) Å).


C17
C16
O6
O5
O1
C4
C8
C5
O3
O4
C3
C15
H40
C7
O2
C6
C1
C2
C10
C9
C14
C13
C11
C12


C17
C16
O5
O6
O1
C4
C8
C5
H4O
O4
C7
C6
O3
C3
C9
O2
C15
C1
C2
C10
C11
C13
C14
C12


05′
06′
01′
02′
04′
03′
H40
04
05
06
01
02
03
04″
H40″
05″
06″
01″
02″
03″

List of Tables

Table 1. Crystallographic Experimental Details

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Table 3. Selected Interatomic Distances

Table 4. Selected Interatomic Angles

Table 5. Torsional Angles

Table 6. Anisotropic Displacement Parameters

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{17}H_{20}O_6$
formula weight	320.33
crystal dimensions (mm)	0.44 × 0.15 × 0.06
crystal system	monoclinic
space group	$P2_1$ (No. 4)
unit cell parameters[a]	
a (Å)	6.0006 (8)
b (Å)	8.0097 (11)
c (Å)	14.4792 (19)
β (deg)	90.680 (2)
V (Å^3)	695.86 (16)
Z	2
ρ_{calcd} (g cm^{-3})	1.529
μ (mm^{-1})	0.116
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (15 s exposures)
data collection 2θ limit (deg)	52.78
total data collected	5359 (-7 ≤ h ≤ 7, -10 ≤ k ≤ 10, -18 ≤ l ≤ 18)
independent reflections	2829 (R_{int} = 0.0291)
number of observed reflections (*NO*)	2480 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method (*SHELXL–93*[d])	full-matrix least-squares on F^2
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9931–0.9508
data/restraints/parameters	2829 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 209
Flack absolute structure parameter[e]	1.8 (10)
goodness-of-fit (S)[f]	1.054 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0363
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.0837
largest difference peak and hole	0.229 and –0.195 e Å^{-3}

[a]Obtained from least-squares refinement of 2470 reflections with $5.62° < 2\theta < 51.68°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. In this case the relatively large standard uncertainty indicates that the structural data alone should not be used to confirm absolute stereochemistry, but should be used in conjunction with the established stereochemistry of the precursor compound.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0292P)^2 + 0.2045P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.0825(2)	0.27625(18)	0.32666(10)	0.0198(3)*
O2	-0.0578(2)	0.20388(18)	0.16385(10)	0.0207(3)*
O3	-0.0902(3)	-0.06594(19)	0.18673(11)	0.0279(4)*
O4	-0.1457(2)	0.5883(2)	0.12893(11)	0.0297(4)*
O5	0.3354(3)	0.1064(2)	0.48518(10)	0.0262(4)*
O6	0.0578(3)	-0.0325(2)	0.40808(10)	0.0258(4)*
C1	0.2671(3)	0.0609(3)	0.22988(13)	0.0171(4)*
C2	0.3526(4)	-0.1130(3)	0.26051(14)	0.0219(5)*
C3	0.4296(4)	-0.0927(3)	0.36128(15)	0.0243(5)*
C4	0.2730(4)	0.0387(3)	0.39810(14)	0.0216(5)*
C5	0.2741(3)	0.1705(3)	0.32082(14)	0.0186(5)*
C6	0.4710(4)	0.2917(3)	0.32536(15)	0.0216(5)*
C7	0.3719(4)	0.4560(3)	0.28768(15)	0.0244(5)*
C8	0.1308(4)	0.4080(3)	0.26301(14)	0.0204(5)*
C9	0.1006(4)	0.3432(3)	0.16243(14)	0.0184(5)*
C10	0.0134(4)	0.4751(3)	0.09346(15)	0.0229(5)*
C11	0.2263(4)	0.5511(3)	0.05506(15)	0.0265(5)*
C12	0.3805(4)	0.4003(3)	0.04274(15)	0.0256(5)*
C13	0.3132(4)	0.2815(3)	0.11852(14)	0.0192(5)*
C14	0.3955(3)	0.1409(3)	0.15079(14)	0.0195(5)*
C15	0.0251(3)	0.0567(3)	0.19402(13)	0.0185(4)*
C16	0.1547(4)	0.0822(3)	0.54801(15)	0.0259(5)*
C17	-0.0429(4)	0.0499(3)	0.48522(15)	0.0281(5)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C5	1.431(2)	C2	C3	1.534(3)
O1	C8	1.433(2)	C3	C4	1.512(3)
O2	C9	1.466(2)	C4	C5	1.539(3)
O2	C15	1.350(3)	C5	C6	1.530(3)
O3	C15	1.205(2)	C6	C7	1.541(3)
O4	O3[a]	2.911(2)[b]	C7	C8	1.535(3)
O4	C10	1.418(3)	C8	C9	1.555(3)
O5	C4	1.419(2)	C9	C10	1.541(3)
O5	C16	1.437(3)	C9	C13	1.515(3)
O6	C4	1.421(3)	C10	C11	1.526(3)
O6	C17	1.436(3)	C11	C12	1.533(3)
C1	C2	1.547(3)	C12	C13	1.511(3)
C1	C5	1.583(3)	C13	C14	1.313(3)
C1	C14	1.529(3)	C16	C17	1.508(3)
C1	C15	1.537(3)	H4O	O3[a]	2.14[b]

[a]At x, $1+y$, z. [b]Nonbonded distance.

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C5	O1	C8	103.25(15)	C6	C7	C8	103.11(18)
C9	O2	C15	115.64(15)	O1	C8	C7	103.43(17)
C4	O5	C16	108.53(16)	O1	C8	C9	109.52(17)
C4	O6	C17	106.64(16)	C7	C8	C9	113.64(17)
C2	C1	C5	104.80(16)	O2	C9	C8	108.04(16)
C2	C1	C14	115.08(17)	O2	C9	C10	108.43(16)
C2	C1	C15	112.69(18)	O2	C9	C13	107.87(17)
C5	C1	C14	112.46(17)	C8	C9	C10	114.39(17)
C5	C1	C15	107.98(16)	C8	C9	C13	114.36(17)
C14	C1	C15	103.82(16)	C10	C9	C13	103.45(17)
C1	C2	C3	105.81(17)	O4	C10	C9	115.39(18)
C2	C3	C4	103.15(17)	O4	C10	C11	116.58(19)
O5	C4	O6	107.06(17)	C9	C10	C11	103.34(18)
O5	C4	C3	114.90(18)	C10	C11	C12	103.71(19)
O5	C4	C5	112.36(17)	C11	C12	C13	104.18(18)
O6	C4	C3	109.05(17)	C9	C13	C12	109.44(18)
O6	C4	C5	111.15(17)	C9	C13	C14	116.46(19)
C3	C4	C5	102.31(17)	C12	C13	C14	134.1(2)
O1	C5	C1	111.35(16)	C1	C14	C13	115.79(18)
O1	C5	C4	110.67(16)	O2	C15	O3	118.32(18)
O1	C5	C6	104.01(17)	O2	C15	C1	115.68(18)
C1	C5	C4	102.95(17)	O3	C15	C1	125.9(2)
C1	C5	C6	113.61(17)	O5	C16	C17	103.62(17)
C4	C5	C6	114.46(17)	O6	C17	C16	102.28(18)
C5	C6	C7	103.43(17)	O4	H4O	O3[a]	152.0[b]

[a]At x, 1+y, z. [b]Angle includes nonbonded O–H···O interaction.

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C8	O1	C5	C1	-76.84(19)	C2	C3	C4	C5	-45.8(2)
C8	O1	C5	C4	169.30(16)	O5	C4	C5	O1	-76.0(2)
C8	O1	C5	C6	45.90(18)	O5	C4	C5	C1	164.94(17)
C5	O1	C8	C7	-46.94(19)	O5	C4	C5	C6	41.1(2)
C5	O1	C8	C9	74.54(19)	O6	C4	C5	O1	44.0(2)
C15	O2	C9	C8	-77.6(2)	O6	C4	C5	C1	-75.1(2)
C15	O2	C9	C10	157.90(17)	O6	C4	C5	C6	161.11(17)
C15	O2	C9	C13	46.5(2)	C3	C4	C5	O1	160.25(16)
C9	O2	C15	O3	-171.67(18)	C3	C4	C5	C1	41.17(19)
C9	O2	C15	C1	4.9(2)	C3	C4	C5	C6	-82.6(2)
C16	O5	C4	O6	-2.0(2)	O1	C5	C6	C7	-26.1(2)
C16	O5	C4	C3	-123.30(19)	C1	C5	C6	C7	95.1(2)
C16	O5	C4	C5	120.26(19)	C4	C5	C6	C7	-146.98(18)
C4	O5	C16	C17	-18.6(2)	C5	C6	C7	C8	-1.7(2)
C17	O6	C4	O5	23.2(2)	C6	C7	C8	O1	28.9(2)
C17	O6	C4	C3	148.12(18)	C6	C7	C8	C9	-89.7(2)
C17	O6	C4	C5	-99.8(2)	O1	C8	C9	O2	25.5(2)
C4	O6	C17	C16	-33.8(2)	O1	C8	C9	C10	146.30(18)
C5	C1	C2	C3	-6.5(2)	O1	C8	C9	C13	-94.6(2)
C14	C1	C2	C3	117.60(19)	C7	C8	C9	O2	140.56(18)
C15	C1	C2	C3	-123.62(19)	C7	C8	C9	C10	-98.6(2)
C2	C1	C5	O1	-139.67(17)	C7	C8	C9	C13	20.5(3)
C2	C1	C5	C4	-21.1(2)	O2	C9	C10	O4	83.7(2)
C2	C1	C5	C6	103.3(2)	O2	C9	C10	C11	-147.84(17)
C14	C1	C5	O1	94.62(19)	C8	C9	C10	O4	-36.9(3)
C14	C1	C5	C4	-146.78(17)	C8	C9	C10	C11	91.5(2)
C14	C1	C5	C6	-22.4(2)	C13	C9	C10	O4	-161.91(17)
C15	C1	C5	O1	-19.3(2)	C13	C9	C10	C11	-33.5(2)
C15	C1	C5	C4	99.27(19)	O2	C9	C13	C12	129.13(18)
C15	C1	C5	C6	-136.37(18)	O2	C9	C13	C14	-49.5(2)
C2	C1	C14	C13	174.18(18)	C8	C9	C13	C12	-110.7(2)
C5	C1	C14	C13	-65.9(2)	C8	C9	C13	C14	70.7(2)
C15	C1	C14	C13	50.6(2)	C10	C9	C13	C12	14.4(2)
C2	C1	C15	O2	-178.32(17)	C10	C9	C13	C14	-164.29(19)
C2	C1	C15	O3	-2.0(3)	O4	C10	C11	C12	168.06(18)
C5	C1	C15	O2	66.4(2)	C9	C10	C11	C12	40.4(2)
C5	C1	C15	O3	-117.3(2)	C10	C11	C12	C13	-31.2(2)
C14	C1	C15	O2	-53.1(2)	C11	C12	C13	C9	10.3(2)
C14	C1	C15	O3	123.1(2)	C11	C12	C13	C14	-171.4(2)
C1	C2	C3	C4	32.2(2)	C9	C13	C14	C1	-1.2(3)
C2	C3	C4	O5	-167.81(17)	C12	C13	C14	C1	-179.5(2)
C2	C3	C4	O6	72.0(2)	O5	C16	C17	O6	31.7(2)

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0223(8)	0.0183(8)	0.0190(7)	0.0011(6)	0.0042(6)	0.0017(6)
O2	0.0178(8)	0.0183(8)	0.0260(8)	0.0003(6)	-0.0015(6)	-0.0018(6)
O3	0.0249(9)	0.0199(9)	0.0389(9)	-0.0033(7)	-0.0055(7)	-0.0059(7)
O4	0.0266(8)	0.0218(9)	0.0407(9)	0.0007(8)	-0.0037(7)	0.0042(7)
O5	0.0305(9)	0.0306(9)	0.0174(7)	-0.0003(7)	0.0002(6)	-0.0077(7)
O6	0.0279(8)	0.0258(9)	0.0239(8)	0.0017(7)	0.0025(6)	-0.0091(7)
C1	0.0182(10)	0.0143(10)	0.0187(10)	-0.0019(9)	-0.0009(8)	-0.0019(9)
C2	0.0235(12)	0.0175(11)	0.0247(11)	-0.0030(9)	-0.0009(9)	0.0007(9)
C3	0.0261(13)	0.0200(12)	0.0267(12)	0.0025(10)	-0.0056(9)	0.0008(10)
C4	0.0237(12)	0.0197(12)	0.0211(11)	0.0005(9)	-0.0035(9)	-0.0050(9)
C5	0.0188(11)	0.0190(11)	0.0180(11)	-0.0015(9)	0.0001(8)	0.0003(9)
C6	0.0239(12)	0.0210(11)	0.0198(11)	0.0007(9)	-0.0009(9)	-0.0045(9)
C7	0.0340(13)	0.0194(12)	0.0198(11)	0.0006(9)	-0.0037(9)	-0.0030(10)
C8	0.0273(12)	0.0154(11)	0.0184(10)	0.0009(9)	0.0018(9)	0.0014(9)
C9	0.0178(11)	0.0155(10)	0.0217(11)	0.0003(8)	-0.0021(8)	-0.0028(9)
C10	0.0258(12)	0.0208(11)	0.0220(11)	0.0003(9)	-0.0026(9)	-0.0003(10)
C11	0.0320(13)	0.0254(13)	0.0220(11)	0.0037(10)	-0.0030(9)	-0.0026(11)
C12	0.0258(12)	0.0316(13)	0.0193(10)	0.0014(10)	0.0016(9)	-0.0022(10)
C13	0.0193(11)	0.0220(11)	0.0163(10)	-0.0042(9)	-0.0013(8)	-0.0035(9)
C14	0.0166(11)	0.0225(12)	0.0195(11)	-0.0043(9)	0.0014(8)	0.0009(9)
C15	0.0208(11)	0.0182(11)	0.0166(10)	-0.0012(9)	0.0015(8)	0.0006(9)
C16	0.0301(12)	0.0265(12)	0.0210(11)	0.0027(10)	0.0023(9)	0.0026(11)
C17	0.0285(13)	0.0302(13)	0.0258(12)	0.0040(11)	0.0042(9)	-0.0009(11)

The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	x	y	z	U_{eq}, Å^2
H4O	-0.0828	0.6791	0.1422	0.045
H2A	0.2319	-0.1970	0.2557	0.026
H2B	0.4780	-0.1492	0.2215	0.026
H3A	0.4149	-0.1988	0.3957	0.029
H3B	0.5864	-0.0547	0.3650	0.029
H6A	0.5951	0.2525	0.2865	0.026
H6B	0.5259	0.3056	0.3897	0.026
H7A	0.3766	0.5449	0.3352	0.029
H7B	0.4529	0.4945	0.2325	0.029
H8	0.0294	0.5049	0.2739	0.024
H10	-0.0609	0.4133	0.0416	0.027
H11A	0.2920	0.6327	0.0989	0.032
H11B	0.1968	0.6073	-0.0047	0.032
H12A	0.3580	0.3488	-0.0188	0.031
H12B	0.5387	0.4333	0.0498	0.031
H14	0.5267	0.0920	0.1265	0.023
H16A	0.1308	0.1829	0.5862	0.031
H16B	0.1834	-0.0144	0.5891	0.031
H17A	-0.1158	0.1555	0.4661	0.034
H17B	-0.1539	-0.0229	0.5153	0.034

APPENDIX D

X-RAY CRYSTALLOGRAPHIC DATA TABLES FOR COMPOUND 26 (CHAPTER 2)

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STRUCTURE REPORT

XCL Code: FGW0502 **Date:** 20 April 2005

Compound: 16,17-Dioxa-4,4-ethylenedioxy-10-hydroxypentacyclo[7.5.2.1^{5,8}.0^{1,5}.0^{9,13}]heptadeca-6,13-dien-15-one (*racemate*)

Formula: $C_{17}H_{18}O_6$

Supervisor: F. G. West

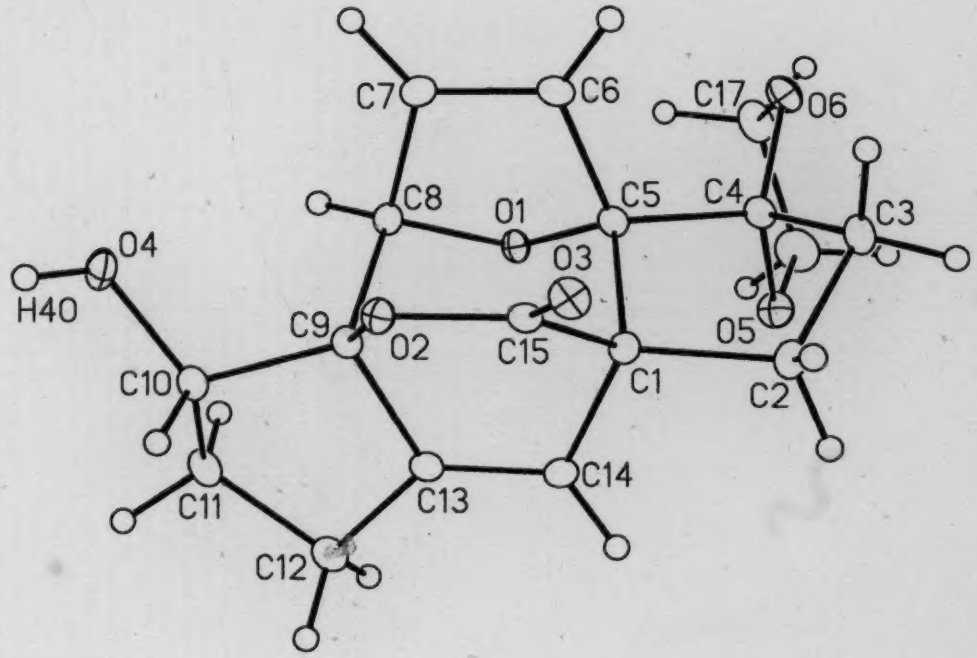
Crystallographer: R. McDonald

Figure Legends

Figure 1. Perspective view of the 16,17-dioxa-4,4-ethylenedioxy-10-hydroxy-pentacyclo[7.5.2.$1^{5,8}$.$0^{1,5}$.$0^{9,13}$]heptadeca-6,13-dien-15-one molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Figure 2. Alternate view of the molecule. Hydrogens of methylene groups have been omitted.

Figure 3. Illustration of hydrogen-bonded interactions between adjacent molecules in the unit cell. Primed atoms are related to unprimed ones via the crystallographic inversion center ($^1/_2$, 0, $^1/_2$).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O6
C8
O1
C5
C4
C3
O4
O3
H40
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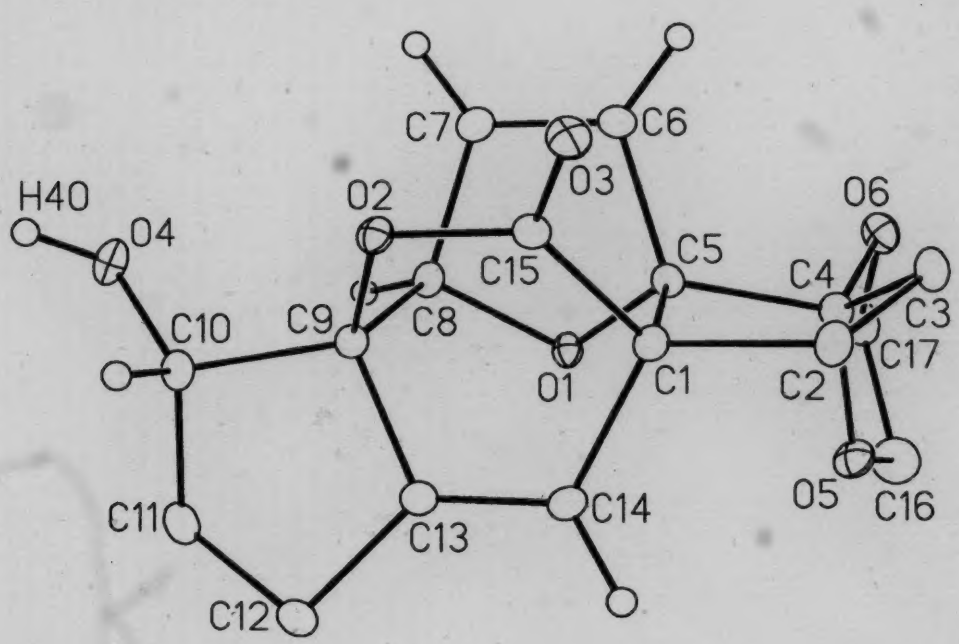
C10
C1
C2
C11
C13
C14
C12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O6
O4
C15
C5
C4
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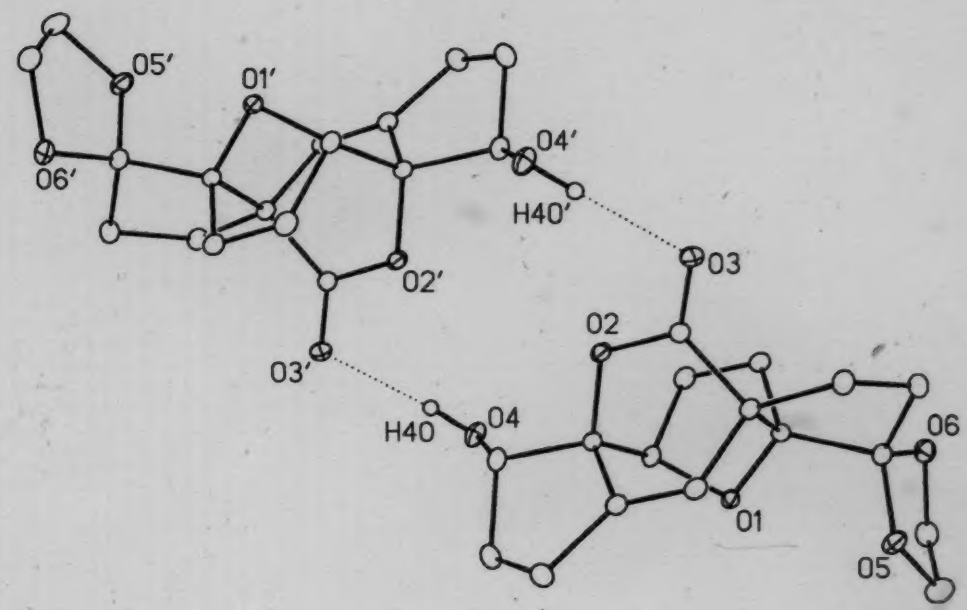
C10
C9
C8
O1
C1
C2
C17
O5
C16
C11
C13
C14
C12


05′
01′
04′
06′
H40′
03
02′
02
03′
H40
04
06
01
05

List of Tables

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Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{17}H_{18}O_6$
formula weight	318.31
crystal dimensions (mm)	0.54 × 0.38 × 0.14
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	11.0011 (13)
b (Å)	12.2123 (15)
c (Å)	11.1592 (13)
β (deg)	97.2768 (18)
V (Å^3)	1487.1 (3)
Z	4
ρ_{calcd} (g cm^{-3})	1.422
μ (mm^{-1})	0.108
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	52.70
total data collected	11487 (-13 ≤ h ≤ 13, -15 ≤ k ≤ 15, -13 ≤ l ≤ 13)
independent reflections	3030 (R_{int} = 0.0271)
number of observed reflections (*NO*)	2615 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method (*SHELXL–93*[d])	full-matrix least-squares on F^2
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9850–0.9440
data/restraints/parameters	3030 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 210
extinction coefficient (x)[e]	0.0115 (13)
goodness-of-fit (S)[f]	1.038 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0352
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.0945
largest difference peak and hole	0.330 and –0.193 e Å^{-3}

[a]Obtained from least-squares refinement of 7559 reflections with $4.96° < 2\theta < 52.70°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0457P)^2 + 0.5966P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.12083(8)	0.00665(7)	0.23459(8)	0.0214(2)*
O2	0.38104(8)	0.05564(7)	0.40613(8)	0.0219(2)*
O3	0.38304(8)	0.23255(8)	0.44136(8)	0.0266(2)*
O4	0.37604(9)	-0.20076(8)	0.43403(9)	0.0318(3)*
O5	0.02912(9)	0.17200(8)	0.08068(9)	0.0304(2)*
O6	-0.08478(8)	0.18323(8)	0.23754(9)	0.0299(2)*
C1	0.25709(11)	0.17043(10)	0.25916(11)	0.0207(3)*
C2	0.22674(12)	0.29117(11)	0.22739(13)	0.0267(3)*
C3	0.08988(13)	0.30591(11)	0.23720(13)	0.0282(3)*
C4	0.03525(12)	0.19387(11)	0.20640(12)	0.0240(3)*
C5	0.12785(11)	0.11600(10)	0.27690(11)	0.0200(3)*
C6	0.11403(11)	0.10184(11)	0.41002(12)	0.0236(3)*
C7	0.15274(12)	0.00236(11)	0.44160(12)	0.0257(3)*
C8	0.19343(11)	-0.05122(11)	0.33125(11)	0.0222(3)*
C9	0.33254(11)	-0.02984(10)	0.32135(11)	0.0202(3)*
C10	0.41186(12)	-0.13193(11)	0.34275(12)	0.0254(3)*
C11	0.39787(14)	-0.18415(12)	0.21742(14)	0.0329(3)*
C12	0.40968(14)	-0.08652(12)	0.13313(13)	0.0320(3)*
C13	0.35109(11)	0.00607(11)	0.19518(12)	0.0230(3)*
C14	0.31664(11)	0.10678(11)	0.16461(11)	0.0231(3)*
C15	0.34381(11)	0.15779(10)	0.37654(11)	0.0204(3)*
C16	-0.09336(15)	0.13926(16)	0.03710(16)	0.0435(4)*
C17	-0.14823(13)	0.11104(13)	0.14962(15)	0.0364(4)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C5	1.4153(15)	C2	C3	1.5340(19)
O1	C8	1.4431(15)	C3	C4	1.5162(19)
O2	C9	1.4634(15)	C4	C5	1.5356(18)
O2	C15	1.3412(15)	C5	C6	1.5223(18)
O3	C15	1.2100(16)	C6	C7	1.320(2)
O4	O3[a]	2.8592(13)†	C7	C8	1.5116(19)
O4	C10	1.4146(17)	C8	C9	1.5700(17)
O5	C4	1.4213(16)	C9	C10	1.5232(18)
O5	C16	1.4303(18)	C9	C13	1.5130(18)
O6	C4	1.4133(16)	C10	C11	1.527(2)
O6	C17	1.4329(18)	C11	C12	1.534(2)
C1	C2	1.5432(18)	C12	C13	1.5121(19)
C1	C5	1.6043(17)	C13	C14	1.3190(19)
C1	C14	1.5237(18)	C16	C17	1.501(2)
C1	C15	1.5274(17)	H4O	O3[a]	2.05†

[a]At $1-x, \bar{y}, 1-z$. †Nonbonded distance.

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C5	O1	C8	102.19(9)	C6	C7	C8	107.43(12)
C9	O2	C15	115.43(9)	O1	C8	C7	101.77(10)
C4	O5	C16	108.24(11)	O1	C8	C9	108.55(10)
C4	O6	C17	106.11(11)	C7	C8	C9	112.16(10)
C2	C1	C5	104.76(10)	O2	C9	C8	110.61(10)
C2	C1	C14	115.33(11)	O2	C9	C10	109.14(10)
C2	C1	C15	112.77(10)	O2	C9	C13	108.28(10)
C5	C1	C14	109.85(10)	C8	C9	C10	113.39(10)
C5	C1	C15	108.62(10)	C8	C9	C13	111.18(10)
C14	C1	C15	105.41(10)	C10	C9	C13	103.94(10)
C1	C2	C3	106.35(11)	O4	C10	C9	113.14(11)
C2	C3	C4	104.03(11)	O4	C10	C11	113.98(12)
O5	C4	O6	107.24(10)	C9	C10	C11	102.06(10)
O5	C4	C3	111.18(11)	C10	C11	C12	103.32(12)
O5	C4	C5	109.55(10)	C11	C12	C13	103.08(11)
O6	C4	C3	112.53(11)	C9	C13	C12	108.96(11)
O6	C4	C5	113.39(11)	C9	C13	C14	116.27(12)
C3	C4	C5	102.97(10)	C12	C13	C14	134.75(13)
O1	C5	C1	111.20(10)	C1	C14	C13	115.55(11)
O1	C5	C4	114.13(10)	O2	C15	O3	118.69(11)
O1	C5	C6	102.14(10)	O2	C15	C1	116.31(10)
C1	C5	C4	102.77(10)	O3	C15	C1	124.97(12)
C1	C5	C6	111.54(10)	O5	C16	C17	103.96(12)
C4	C5	C6	115.37(11)	O6	C17	C16	102.65(12)
C5	C6	C7	107.24(12)	O4	H4O	O3[a]	161.1[†]

[a]At 1–x, $\bar{y}$, 1–z. [†]Angle includes nonbonded O–H···O interaction.

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C8	O1	C5	C1	77.55(11)	C2	C3	C4	C5	43.66(13)
C8	O1	C5	C4	-166.76(10)	O5	C4	C5	O1	-42.19(14)
C8	O1	C5	C6	-41.54(11)	O5	C4	C5	C1	78.33(12)
C5	O1	C8	C7	41.74(11)	O5	C4	C5	C6	-160.06(10)
C5	O1	C8	C9	-76.70(11)	O6	C4	C5	O1	77.57(14)
C15	O2	C9	C8	-72.86(13)	O6	C4	C5	C1	-161.92(10)
C15	O2	C9	C10	161.73(10)	O6	C4	C5	C6	-40.31(15)
C15	O2	C9	C13	49.19(13)	C3	C4	C5	O1	-160.56(10)
C9	O2	C15	O3	-178.18(11)	C3	C4	C5	C1	-40.04(12)
C9	O2	C15	C1	-0.23(15)	C3	C4	C5	C6	81.57(13)
C16	O5	C4	O6	-4.62(15)	O1	C5	C6	C7	25.99(13)
C16	O5	C4	C3	-128.02(13)	C1	C5	C6	C7	-92.86(13)
C16	O5	C4	C5	118.83(13)	C4	C5	C6	C7	150.38(11)
C4	O5	C16	C17	-16.36(16)	C5	C6	C7	C8	0.27(14)
C17	O6	C4	O5	24.97(14)	C6	C7	C8	O1	-25.86(13)
C17	O6	C4	C3	147.53(12)	C6	C7	C8	C9	89.97(13)
C17	O6	C4	C5	-96.09(13)	O1	C8	C9	O2	99.33(11)
C4	O6	C17	C16	-34.24(14)	O1	C8	C9	C10	-137.70(11)
C5	C1	C2	C3	4.39(13)	O1	C8	C9	C13	-21.01(14)
C14	C1	C2	C3	125.27(12)	C7	C8	C9	O2	-12.32(14)
C15	C1	C2	C3	-113.57(12)	C7	C8	C9	C10	110.65(12)
C2	C1	C5	O1	144.25(10)	C7	C8	C9	C13	-132.66(12)
C2	C1	C5	C4	21.74(12)	O2	C9	C10	O4	86.14(13)
C2	C1	C5	C6	-102.44(12)	O2	C9	C10	C11	-150.95(10)
C14	C1	C5	O1	19.81(13)	C8	C9	C10	O4	-37.64(15)
C14	C1	C5	C4	-102.70(11)	C8	C9	C10	C11	85.27(13)
C14	C1	C5	C6	133.12(11)	C13	C9	C10	O4	-158.50(11)
C15	C1	C5	O1	-95.00(12)	C13	C9	C10	C11	-35.59(13)
C15	C1	C5	C4	142.49(10)	O2	C9	C13	C12	130.72(11)
C15	C1	C5	C6	18.30(14)	O2	C9	C13	C14	-48.20(14)
C2	C1	C14	C13	175.14(11)	C8	C9	C13	C12	-107.57(12)
C5	C1	C14	C13	-66.79(14)	C8	C9	C13	C14	73.51(15)
C15	C1	C14	C13	50.06(14)	C10	C9	C13	C12	14.76(14)
C2	C1	C15	O2	-175.70(11)	C10	C9	C13	C14	-164.16(11)
C2	C1	C15	O3	2.10(18)	O4	C10	C11	C12	165.95(11)
C5	C1	C15	O2	68.63(13)	C9	C10	C11	C12	43.61(13)
C5	C1	C15	O3	-113.56(13)	C10	C11	C12	C13	-34.15(14)
C14	C1	C15	O2	-49.04(14)	C11	C12	C13	C9	11.98(15)
C14	C1	C15	O3	128.76(13)	C11	C12	C13	C14	-169.38(15)
C1	C2	C3	C4	-29.49(14)	C9	C13	C14	C1	-2.94(17)
C2	C3	C4	O5	-73.57(13)	C12	C13	C14	C1	178.50(14)
C2	C3	C4	O6	166.11(11)	O5	C16	C17	O6	30.76(16)

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0193(4)	0.0198(4)	0.0237(5)	-0.0010(3)	-0.0030(3)	0.0007(3)
O2	0.0203(4)	0.0237(5)	0.0203(4)	-0.0003(4)	-0.0027(3)	-0.0009(4)
O3	0.0243(5)	0.0270(5)	0.0273(5)	-0.0053(4)	-0.0016(4)	-0.0024(4)
O4	0.0276(5)	0.0304(6)	0.0352(6)	0.0111(4)	-0.0043(4)	-0.0004(4)
O5	0.0270(5)	0.0384(6)	0.0236(5)	0.0012(4)	-0.0050(4)	0.0005(4)
O6	0.0175(5)	0.0344(5)	0.0369(6)	-0.0024(4)	0.0000(4)	0.0027(4)
C1	0.0184(6)	0.0219(6)	0.0211(6)	0.0014(5)	0.0000(5)	-0.0012(5)
C2	0.0250(7)	0.0229(7)	0.0312(7)	0.0035(5)	-0.0009(5)	-0.0007(5)
C3	0.0267(7)	0.0232(7)	0.0337(7)	0.0004(6)	-0.0007(6)	0.0045(5)
C4	0.0195(6)	0.0267(7)	0.0251(7)	-0.0002(5)	-0.0003(5)	0.0026(5)
C5	0.0171(6)	0.0205(6)	0.0219(6)	-0.0023(5)	0.0000(5)	-0.0002(5)
C6	0.0176(6)	0.0314(7)	0.0220(6)	-0.0026(5)	0.0031(5)	-0.0008(5)
C7	0.0200(6)	0.0330(7)	0.0243(7)	0.0041(5)	0.0040(5)	-0.0024(5)
C8	0.0181(6)	0.0229(6)	0.0247(6)	0.0035(5)	-0.0003(5)	-0.0005(5)
C9	0.0182(6)	0.0220(6)	0.0198(6)	-0.0014(5)	-0.0003(5)	0.0000(5)
C10	0.0196(6)	0.0260(7)	0.0298(7)	0.0032(5)	0.0002(5)	0.0025(5)
C11	0.0331(8)	0.0296(7)	0.0359(8)	-0.0035(6)	0.0042(6)	0.0096(6)
C12	0.0330(8)	0.0363(8)	0.0272(7)	-0.0033(6)	0.0064(6)	0.0083(6)
C13	0.0191(6)	0.0294(7)	0.0202(6)	-0.0007(5)	0.0017(5)	0.0003(5)
C14	0.0209(6)	0.0298(7)	0.0185(6)	0.0019(5)	0.0023(5)	-0.0009(5)
C15	0.0164(6)	0.0238(6)	0.0213(6)	-0.0005(5)	0.0038(5)	-0.0014(5)
C16	0.0329(8)	0.0534(10)	0.0406(9)	-0.0099(8)	-0.0101(7)	-0.0030(7)
C17	0.0243(7)	0.0313(8)	0.0511(10)	-0.0054(7)	-0.0046(6)	-0.0013(6)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H4O	0.4380	-0.2182	0.4822	0.048
H2A	0.2764	0.3406	0.2844	0.032
H2B	0.2440	0.3078	0.1444	0.032
H3A	0.0769	0.3280	0.3200	0.034
H3B	0.0532	0.3618	0.1794	0.034
H6	0.0833	0.1547	0.4609	0.028
H7	0.1547	-0.0297	0.5194	0.031
H8	0.1744	-0.1313	0.3287	0.027
H10	0.4992	-0.1095	0.3653	0.030
H11A	0.3170	-0.2201	0.1989	0.039
H11B	0.4631	-0.2388	0.2108	0.039
H12A	0.4967	-0.0704	0.1261	0.038
H12B	0.3656	-0.1004	0.0516	0.038
H14	0.3282	0.1376	0.0887	0.028
H16A	-0.0935	0.0750	-0.0170	0.052
H16B	-0.1390	0.1997	-0.0073	0.052
H17A	-0.2376	0.1251	0.1394	0.044
H17B	-0.1331	0.0334	0.1724	0.044